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PERIARTERITIS NODOSA

A Report of Two Cases, One with Special Reference to Sensitivity Factors

ANDREW W. CONTRATTO, M.D.

BOSTON

AN ENORMOUS amount of medical literature has been published on the subject of periarteritis nodosa since the disease was first described by Kussmaul and Maier in 1865.[1] Many authors have made a systematic study of the literature and of the disease, the most complete being the articles by Dr. Linn J. Boyd,[2] of the New York Medical College, who wrote an excellent series of eight papers during the years 1938 to 1944.

Within recent years an etiologic agent has been suspected by several investigators. In 1936 Cohen and others [3] reported 2 cases in which the disease was associated with a definite family history of allergy and in which allergic manifestations preceded the onset. They stated in this report: "Our experience with this condition has led us to the conclusion that it is a manifestation of clinical allergy of so severe a degree that irreversible and destructive lesions appear in the blood vessels and lead to disturbances in the function of the organs supplied by the involved vessels." Rackemann and Greene [4] pointed to the presence of asthma in

From the departments of hygiene and medicine, Harvard University, and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbue Brightü und rapid forschreitender allegemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1865.

2. Boyd, L. J.: I. The Clinical Aspects of Periarteritis Nodosa, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **1**:219 (Dec.) 1939; II. The Clinical Aspects of Periarteritis Nodosa, ibid. **3**:32 (April) 1940; III. Periarteritis Nodosa: Cutaneous Symptoms, ibid. **3**:175 (Oct.) 1940; IV. Periarteritis Nodosa: Neuromyositic Manifestations, ibid. **3**:272 (Dec.) 1940; V. Periarteritis Nodosa: Abdominal Manifestations, ibid. **4**:27 (April) 1941; VI. The Renal and Cardiac Manifestations of Periarteritis Nodosa, ibid. **4**:176 (Dec.) 1941; VII. The Cerebral and Ocular Manifestations of Periarteritis Nodosa, ibid. **6**:130 (Oct.) 1943; VIII. Pulmonary Manifestations of Periarteritis Nodosa, ibid. **7**:94 (Oct.-Dec.) 1944.

3. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 (Nov. 7) 1936.

4. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, Tr. A. Am. Physicians **54**:112, 1939.

cases of periarteritis nodosa, as did also Wilson and Alexander,[5] who found that bronchial asthma antedated periarteritis nodosa in almost every instance in the 18 per cent of 300 cases of asthma which they studied.

It is a temptation to discuss in detail the interesting and numerous papers of recent years in which the sulfonamide compounds are suspected of being an inciting factor in the disease. One of interest was published in the *Lancet* in 1945 by Rosenak and Maschmeyer.[6] Of special interest, however, is work done by Rich in Baltimore at the Johns Hopkins Hospital. In 1942, he stated[7]:

> Vascular lesions characteristic of periarteritis nodosa have been found in the viscera of five patients who, shortly before death, had had hypersensitive reactions following therapeutic injections of foreign serum. Four of these patients had received sulfonamides, but in at least two of those cases the evidence indicates that the hypersensitive reaction was serum sickness and not drug hypersensitivity.

In February 1943 Rich[8] stated that typical diffuse periarteritis nodosa had been produced experimentally by establishing in rats a condition analogous to serum sickness in man and that these experiments demonstrate that periarteritis nodosa is one manifestation of the anaphylactic type of sensitivity. In 1945 the same author reported evidence that hypersensitivity to chemicals other than foreign serum or sulfonamide compounds has been demonstrated.[9] A patient with hyperthyroidism was being treated with iodine at the Johns Hopkins Hospital. A severe hypersensitive reaction developed with fever and considerable dermatitis. After a short, stormy course, the patient died, and at autopsy infiltrations of mononuclear cells and eosinophils were observed in various organs and also many fresh lesions of periarteritis nodosa. In this same article Rich recalls that twenty years before, Gruber[10] had suggested that periarteritis nodosa might be the result of hypersensitivity

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5. Wilson, K. S., and Alexander, H. L.: The Relation of Periarteritis Nodosa to Bronchial Asthma and Other Forms of Human Hypersensitivity, J. Lab. & Clin. Med. **30**:195 (March) 1945.

6. Rosenak, B. D., and Maschmeyer, R. H.: Periarteritis Nodosa, Possibly Due to Sulphadiazine Sensitivity, Lancet **1**:305 (March 10) 1945.

7. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123 (Sept.) 1942.

8. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, ibid. **72**:65 (Feb.) 1943.

9. Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarteritis Nodosa (Lewis Linn McArthur Lecture), Proc. Inst. Med. Chicago **15**:270 (March 15) 1945.

10. Gruber, G. B.: Periarteritis Nodosa with Especial Regard to Affection of Gallbladder and Kidneys, Virchows Arch. f. path. Anat. **258**:441, 1925.

and that in 1937 Clark and Kaplan [11] had described 2 cases of lobar pneumonia in which serum sickness developed shortly before death after treatment with serum. In these cases lesions of periarteritis nodosa were present at autopsy. Reimann [12] reported 2 cases in which the patients had trichinosis, and he suggested a relationship to the high degree of anaphylactic reaction to the trichina antigen.

Moschcowitz,[13] in a recent and impressive essay on the biology of periarteritis nodosa, called attention to the reports of Masugi and his co-workers,[14] who produced both glomerulonephritis and periarteritis nodosa in animals sensitized to egg white by injecting the antigen into the general circulation and directly into the renal vein.

In his book, "Essentials of Clinical Allergy," Taub [15] wrote, in reference to periarteritis nodosa: "It is very likely that this disease is a manifestation of a hypersensitivity similar to drug allergy, serum sickness, or bacterial allergy with the allergic response occurring in the blood vessel walls as a result of the union of antigen and reagin in these tissues." This author found that a high blood eosinophil content is usually present, as evidenced by the 2 cases which he reports, in 1 of which it reached 60 per cent and in the other 70 per cent.

With this concept of the etiologic factor in the causation of periarteritis nodosa, 2 cases are presented, 1 of which is believed to demonstrate the hypersensitivity of a person to a condition heretofore not specifically stated, namely cervical glandular tuberculosis. The difficulty in diagnosis, the clinical course and the prognosis for this patient who is now alive and well have been most unusual. The second patient, in whom the course of the disease contrasted markedly to that in the first and in whom no specific etiologic factor could be demonstrated, died suddenly.

CASE 1.—F. C., with quiescent periarteritis nodosa, is a Chinese who at the time of the writing of this paper is alive and well at the age of 40 and teaching in Canton, China, as associate professor of chemistry at the University of Canton.

He was born in San Francisco. His mother died of a "heart attack" at the age of 50, but his father and four brothers and four sisters are living and well. There was no history of tuberculosis, diabetes, cancer, allergy, epilepsy, insanity or

11. Clark, E., and Kaplan, B. I.: Endocardial, Arterial, and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458 (Oct.) 1937.

12. Reimann, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa: Differential Diagnosis; Possible Relationship, J. A. M. A. **122**:274 (May 29) 1943.

13. Moschcowitz, E.: Essays on the Biology of Disease: Periarteritis Nodosa, J. Mt. Sinai Hosp. **12**:1054 (March-April) 1946.

14. Masugi, M., and Isibasi, T.: Ueber allergische Vorgänge bei Allgemeininfektion vom Standpunkt der experimentellen Forschung, Beitr. z. path. Anat. u. z. allg. Path. **96**:391, 1936. Masugi, M., and Sato, Y.: Ueber die allergische Gewebsreaktion der Niere, Virchows Arch. f. path. Anat. **293**:615, 1934.

15. Taub, S. J.: Essentials of Clinical Allergy, Baltimore, Williams & Wilkins Company, 1945, pp. 168-169.

hemophilia in the family. He had been married for fourteen years and had three children, aged 11, 9 and 4 years. As a child, he had attacks of measles, mumps, whooping cough and chickenpox. Scarlet fever, typhoid, rheumatic fever, bronchitis, pneumonia and pleurisy were not reported.

In 1927, before the patient was seen by my colleagues and me, he entered a sanatorium at Saranac Lake, N. Y., with a diagnosis of bilateral apical tuberculosis. Before this, there was cough, fever, night sweats, rather extensive hemoptysis (1 cupful) and some loss in weight. He was treated without pneumothorax or other collapse therapy and was discharged at the end of a year with his illness arrested; he has had no recurrence up to the present time. Since then the process has been apparently arrested as seen in numerous subsequent roentgenograms.

One pertinent episode which occurred during his stay in Saranac was recalled by the patient. He had a flare-up of fever, and red, tender nodules appeared on the lateral and posterior aspects of both legs, accompanied with pains in the ankle joints. He estimated that the duration of these symptoms was about three weeks.

The patient was first seen by us at the Stillman Infirmary on Sept. 20, 1939. At this time his chief complaints were double vision, headache (paroxysmal in nature and suggestive of migraine), nausea and vomiting. A physical examination revealed no abnormalities. A roentgenogram of the chest showed extensive healed tuberculosis, easily explained by the patient's history. The urine and blood counts were normal. The sedimentation rate of the blood was markedly increased. It is to be noted that whenever the sedimentation rate was determined it was found to be increased to from two to three times normal. Over a period of many years, from 1939 to 1946, whether the patient was experiencing an acute attack or was in a state of recovery this finding was apparent. A roentgenogram of his skull was noncontributory, as were also an electroencephalogram and a lumbar puncture. The headache continued during the patient's stay in the Infirmary. After three days he was discharged with a diagnosis of migraine, which seemed to be relieved by a mixture of sodium salicylate and sodium bromide.

The patient was readmitted to the Stillman Infirmary on the following dates: Oct. 23, 1939 (no diagnosis), Nov. 4, 1939 (diagnosis, migraine) and March 30, 1940 (diagnosis, fatigue, with infection of the upper respiratory tract). In each instance he was hospitalized for from three to seven days and his symptoms were as previously described.

When he was readmitted to the Infirmary on April 22, 1941, he was complaining of fever, sore throat and general malaise. His temperature was 100 F., and there was some nasal congestion and a moderately red throat; a few small cervical glands were noted on both sides. The remainder of the physical examination revealed nothing significant. However, as noted previously, the sedimentation rate showed an increase of about three times normal. On May 9, while still in the Infirmary, the patient complained of some stiffness in his right temporomandibular joint. On examination a large gland was noted, simulating closely the clinical picture of mumps. He remained in the hospital for thirty days with an irregular fever, the temperature being as high as 101 F. during the first twenty days of his illness. It gradually subsided and returned to normal five days before his discharge, at which time no definite diagnosis had been made.

On May 20, 1941, the patient was readmitted to the Infirmary, stating that three days before this date he again noticed fever, general malaise and recurrence of the swelling on the right side of his neck. Physical examination again showed no abnormalities, with the exception of the gland in the neck, and as before the sedimentation rate was increased. On June 4, while he was still in the hospital, some small nodes the size of buckshot were noted under the skin on the right forearm. One of these was removed, and a histologic section proved it to be a lesion of

periarteritis nodosa. The white blood cell count on June 12 was 13,500, and the urine was normal.

On June 19, 1941, the patient was transferred to the Peter Bent Brigham Hospital, where he remained for six days. During his stay there, his temperature continued to be elevated although never exceeding 101 F. The physical condition remained as before. When he was discharged from the Peter Bent Brigham Hospital, the diagnosis was as follows: pulmonary tuberculosis (inactive), tuberculosis of cervical lymph nodes and periarteritis nodosa. The prognosis was considered decidedly unfavorable, and he was advised to return to his home in California for complete rest. He carefully followed the advice given to him and spent three months in a sanatorium, with a continued slow improvement in his health. At the end of this time he was discharged feeling well. He returned to Harvard University and continued his work as a research chemist, remaining well, with some weight increase, until July 28, 1942, when he was seen again at the Infirmary with his usual symptoms. His temperature was 100 F. and his throat moderately red, and at the temporomandibular angle at the left side of the neck there was a node the size of an almond, easily palpable. He remained in the Infirmary for five days, during which time his temperature came down to normal and the swelling in his neck subsided. He was symptom free for only three days after his discharge, and on Aug. 5, 1942, he was readmitted with the same complaints as previously—fever, sore throat and general malaise. His temperature was 101 F., and for the next thirty days it remained elevated, although never going any higher. There were several easily palpable cervical glands. His sedimentation rate was markedly increased, as usual. On August 18 his white blood cell count was 12,300 and the urine was normal. At one time during this period there was the questionable appearance of small nodes in the left arm, which were not large enough for biopsy. At this time the patient complained of aches and pains in the legs, which were not severe in nature but which persisted for one week. He remained in the Infirmary until Oct. 1, 1942, at which time he returned to his duties as a chemist and carried on fulltime activities with the exception of a short period of hospitalization in April 1943 for a perianal abscess. Although the diagnosis was periarteritis nodosa when he was discharged from the Infirmary in October 1942, there was no evidence of a wasting or chronic disease manifested either by symptoms or by physical signs. The sedimentation rate, however, continued to be increased to about three times normal.

On April 28, 1944, the patient was again admitted to the Infirmary with a recurrence of the symptoms for which he had been hospitalized so many times before. At this time his temperature was 101 F., the urine and blood counts were normal and a roentgenogram of his chest showed no change. Several days later enlargement of the posterior cervical lymph nodes developed on the right side of his neck. He again complained of aches and pains in his legs, and loss of weight was conspicuous. On May 9, 1944, he was transferred to the Peter Bent Brigham Hospital for further study. He continued to have fever, and the nodes in his neck became larger than at any time during his illness. Nodes the size of buckshot again developed under the skin of the left arm, one of which was excised and revealed active periarteritis nodosa. A node from the right side of the neck was also excised, and biopsy showed active tuberculosis. The finding of active tuberculosis in a patient with periarteritis nodosa was of the utmost importance and interest and will be discussed later. Throughout his stay at the Peter Bent Brigham Hospital (until July 3, 1944, when he was transferred to Stillman Infirmary for convalescence) he had low grade fever, the temperature ranging in general between 99 and 100 F. in the evening. Malaise slowly decreased, but the nodes in his neck remained tender and swollen. About three weeks after his admission to the hospital, he began to note transitory vague

muscular pains similar to the pains he had had before. When he was discharged on the fifty-seventh day in the hospital, he felt subjectively that his muscular aches and pains were definitely decreasing. There was little change revealed by the physical examination, but his condition was improved, although the diagnosis was inactive pulmonary tuberculosis, tuberculosis of cervical lymph nodes and periarteritis nodosa. During his convalescence at the Stillman Infirmary, he remained afebrile and gradually gained strength and weight. On the day of his discharge, on July 27, 1944, he felt well, had no fever or symptoms of any nature and the glands in his neck were hardly palpable. After a week's vacation in New Hampshire, he returned to his laboratory, working eight hours daily.

Since the last-mentioned date, he has been a patient at the Stillman Infirmary four times, and the following diagnoses were made:

Jan. 4 to Jan. 8, 1945:
Diagnosis: infection of the upper respiratory tract, arrested pulmonary tuberculosis, quiescent cervical tuberculous adenitis and inactive periarteritis nodosa

June 1 to June 7, 1945:
Diagnosis: arrested pulmonary tuberculosis, inactive periarteritis nodosa and Meniere's disease (?)

March 25 to March 31, 1946:
Diagnosis: arrested pulmonary tuberculosis, quiescent cervical tuberculous adenitis and inactive periarteritis nodosa

April 20 to May 18, 1946:
Diagnosis: arrested pulmonary tuberculosis, questionably active cervical tuberculous adenitis and inactive periarteritis nodosa

The latest roentgenogram of the chest was taken on March 26, 1946, and showed no change since the last observation. During the four periods of hospitalization mentioned, the patient was only mildly ill; he was slightly febrile at times, but we felt most assured that his periarteritis nodosa was definitely arrested.

It is to be noted that he never had hypertension or an abnormal urine at any time during his years of illness.

On Aug. 15, 1946, when last seen by us for a check-up, he felt well, looked well and had no symptoms. It was at this time that he advised us of the post offered him in China, and it was agreed that there was no reason why he should not accept it.

CASE 2.—G. H., who died suddenly in London of periarteritis nodosa, was a Chinese of 28 years of age. He went abroad in November 1946 feeling well, and, although he had been seen by us previous to this time, the presence of periarteritis nodosa, though strongly suspected, had not been confirmed.

He was born in Canada of Chinese parents, who are alive and well and living in China. He stated that he had one brother living in Canada and one brother who died at the age of 35 years from an unknown cause. He also had three sisters.

The patient's childhood had been uncomplicated by even the usual diseases, and the only history of illness was an appendectomy performed at the age of 23, at which time he also had bronchial pneumonia. In retrospect, it is interesting to note that the appendectomy was performed because of abdominal pain (the patient's chief complaint throughout the present illness), and although we have attempted to obtain further information from the hospital we have been unsuccessful.

In January 1946 he married a Chinese girl of his own age who was born in New York city.

He was a patient at the Stillman Infirmary for the first time in October 1943, at which time the diagnosis was "infection of the upper respiratory tract." His slight temperature elevation quickly subsided, permitting him to leave the hospital in three days.

When next admitted to the Infirmary on June 16, 1946, the patient complained of pain in the left side and flank, similar to the pain suggestive of nephrolithiasis.

He had had the first attack of this discomfort about three weeks previous to his hospitalization, but after a day or two it had abated. The physical examination at this time revealed nothing significant except for some tenderness in the area of the left costovertebral angle. Intravenous pyelograms and genitourinary studies revealed no abnormalities. Several days later, the pain began to shift more toward the abdomen, and the patient was transferred to the Peter Brent Brigham Hospital. Here a physical examination proved to be noncontributory with the exception that the sedimentation rate was increased by two to three times normal. No abnormalities were found by roentgenologic examination of the stomach and colon. The patient complained of pain down both legs, but a neurologic examination showed nothing abnormal. After two days, he was discharged from the hospital to his home with a deferred diagnosis, but he returned to the Stillman Infirmary the following day, June 22, 1946, reporting a good deal of pain and discomfort, mainly in the abdomen. His temperature was 101 F. There was some tenderness in the upper region of the epigastrium. Otherwise, with the exception of fever and an elevated sedimentation rate, the physical condition remained normal until July 5, when his blood pressure rose to 150 systolic and 110 diastolic and his white blood cell count to 13,900; there were a few red blood cells in the urine. On July 12 it was felt that the fever and general picture were consistent with a diagnosis of periarteritis nodosa, and because of continued abdominal pain the patient was again transferred to the Peter Bent Brigham Hospital for further study. The gallbladder, a series of gastrointestinal roentgenograms, a motility series and one made after a barium enema all were normal. On July 16 the sedimentation rate was increased to four times normal, although the temperature and blood pressure subsided to within normal limits. There was a transitory elevation of the white blood cell count; for instance, on July 12 it was 14,000, with 9 to 10 per cent eosinophils. The electrocardiogram taken on July 18 showed conspicuous deviation from the previous normal records. It showed an abnormal form of ventricular complex, and the T waves in leads II and III were inverted. These tracings were suggestive of coronary artery diesase. By this time it was noted that the patient had suffered a weight loss of 18 pounds (8 Kg.). It was also noted that there were one or two nodules in the vicinity of the brachial artery, not attached to the artery. One of these nodules was excised, and a small piece of the biceps muscle was removed. On examination by the pathologist no abnormality was found.

Within two or three weeks the symptoms abated, the temperature became normal and the patient was discharged from the Peter Bent Brigham Hospital with a tentative diagnosis of periarteritis nodosa.

When last heard from personally, in September 1946, he was in New York and feeling well. Following this communication, he left for London to attend a United Nations Conference but became ill and was admitted to St. Bartholomew's Hospital on November 20. His history at this time was that he had had headache for the previous week and on three occasions convulsive seizures. His blood pressure one week before his admission to the hospital was stated to have been 110 systolic and 70 diastolic. The following is an excerpt from a letter written to us by Dr. G. W. Hayward, of London: "On admission his temperature was subnormal, and there was slight neck rigidity, marked spasm of the abdominal muscles and absent ankle jerks. He was incontinent of urine. His blood pressure was 260 systolic and 160 diastolic. There was no retinitis, and the urine showed a considerable amount of albumin, pus cells and occasional red blood cells. His white blood cell count was 22,000, of which 86 per cent were polymorphonuclear leukocytes. Lumbar puncture showed normal cerebrospinal fluid. His headaches increased, and after three days he complained of marked pain in the left renal angle. His white blood cell count

remained elevated, and edema of the left loin appeared twenty-four hours later. He was afebrile at this time.

"In view of the renal tenderness, renal edema, leukocytosis and urinary changes, it was thought that he had a left perinephric abscess, and the left kidney was explored. At operation there was a large perirenal hematoma containing about 3 pints (1,419 cc.) of blood, and the left kidney was studded with small white infarcts. Following operation his blood pressure was raised to 280 systolic and 170 diastolic, and bilateral papilledema with retinal hemorrhages developed. The blood urea was 66 mg. per hundred cubic centimeters, and the urinary findings were as before. There was a recurrence of bleeding, and a left nephrectomy was carried out, but the patient died two days after operation.

"Autopsy confirmed the diagnosis of periarteritis nodosa. The kidneys showed multiple small infarcts, and there were small aneurysms in the mesenteric vessels, both coronary vessels and middle cerebral artery. There was still a small left renal hematoma.

"The interesting features of this patient were the sudden development of a severe degree of hypertension, the marked leukocytosis without eosinophilia and the cerebral symptoms which caused his admission to the hospital."

SYMPTOMATOLOGY

The symptomatology of periarteritis nodosa is such that it is unwise to list symptoms and signs as being characteristic of this illness. The overemphasis on the cardinal symptoms of the illness has in the past been responsible for the lack of diagnosis in many cases. This is primarily an arterial disease, and the symptoms depend on the organs involved. In the case of F. C., the migraine of which he complained in all probability was due to involvement of some of the cerebral arteries. He evidently had no involvement of the pulmonary or renal arteries and therefore had no asthma or evidence of renal insufficiency. Frequent blood pressure readings were always in the normal range, and at no time during his frequent hospitalizations did he have leukocytosis. Moreover, he never complained of abdominal pain or discomfort, which would lead to the belief that there was no involvement of arteries supplying the abdominal organs. F. C.'s main symptoms were weakness and fever with, at times, indefinite pains in the extremities. It would seem from his whole clinical picture that the arteries involved were probably those of the brain and the superficial arteries supplying the muscles of the extremities.

In contrast, G. H.'s symptoms were those of involvement of arteries supplying the abdominal organs (as manifested by abdominal pain), arteries supplying the muscles of the legs (causing muscular pain) and finally arteries involving he kidneys resulting in considerable renal impairment, hypertension and death.

The incidence of renal impairment in the literature is listed as high as 80 per cent.[16] Eighty-three of Gruber's 115 patients had renal insuffi-

16. (*a*) Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936. (*b*) Footnote 2.

ciency. It must be remembered that in most of these cases the diagnosis was made at autopsy and that renal impairment was the cause of death. It is apparent that the incidence of this impairment will decline as the diagnosis is made in more instances before death.

DIAGNOSIS

The diagnosis of periarteritis nodosa is difficult of establishment in many instances because in the past the cardinal signs and symptoms of fever, eosinophilia, asthma and renal insufficiency were overemphasized. It is obvious that the symptomatology and the clinical findings are largely related to the arteries involved and to changes in the anatomic structures supplied by these arteries. In the case of F. C., the only consistent symptom was fever. There was no asthma, no evidence of renal insufficiency, no hypertension and no leukocytosis. The diagnosis in this case could easily have been overlooked had it not been for repeated thorough physical examinations and the fact that a great deal of importance was placed on the discovery of a small nodule.

In the case of G. H., although the presence of periarteritis nodosa was strongly suspected before death the diagnosis was not definitely made because the biopsy of a small nodule did not reveal the disease. In retrospect, a biopsy of material from the gastrocnemius muscle may have yielded a definite diagnosis, especially in view of the fact that the patient complained of rather severe pain in both legs. Moreover, the cardinal signs and symptoms of fever, leukocytosis, eosinophilia, renal insufficiency and hypertension did not make their appearance until shortly before death, although a mild degree of leukocytosis and eosinophilia of a transitory nature was apparent while the patient was confined to the Peter Bent Brigham Hospital. The symptomatology in the early part of the illness simulated at times that of a condition within the abdomen requiring surgical treatment, and one might have been led to do an exploratory laparotomy.

In a study of a series of cases of periarteritis nodosa, Spiegel [16a] stated that "abdominal pain not adequately explained by the involvement of a single organ was the most presenting symptom." In 2 of her cases the diagnosis was made unexpectedly by a demonstration of the lesions in the appendix following appendectomy. Other authors also report that diagnosis was made by finding the lesions of periarteritis nodosa in various abdominal organs following operation.[17] The definite diagnosis of periarteritis nodosa before death has been made in only about 15 per cent of the cases reported. In the other 85 per cent the diagnosis has been made at autopsy. In Spiegel's [16a] series of 17 cases, the diagnosis was made, as previously stated, in 2 of them by a demonstration of the lesions in the appendix, and in the other 15 the diagnosis

17. Spiegel.[16a] Gruber.[10]

was made at autopsy. Bernstein's [18] report bears out the experience of the authors already referred to in the relationship between the antemortem and postmorten diagnoses.

The value of the sedimentation rate in the diagnosis of periarteritis nodosa has not been definitely established. However, in both of the patients under discussion in this report the sedimentation rate was constantly increased despite the fact that all other clinical and laboratory examinations gave normal results.

The diagnosis is difficult of establishment due to the complexity of the clinical picture, but it is apparent that as physicians become more aware of this illness and as a more thorough investigation is made in patients suspected of having this condition the instances of antemortem diagnosis will increase. However, periarteritis nodosa is to be considered as a possibility in any continued illness, and while the symptoms may be related to any of the organs involved, no symptoms of any one disease may be present. In some cases the diagnosis can be confirmed by biopsy of a subcutaneous nodule, by biopsy of material from the gastrocnemius muscle or by laparotomy.

ETIOLOGY

The etiology of periarteritis nodesa is not definitely established, although the work of Rich, Cohen, Rackemann and others seems to point to the fact that the most likely cause of this condition is an allergic manifestation. In the case of F. C., it is my opinion that the disease was an allergic response to active glandular tuberculosis. The course of his illness and the definite, apparently coincidental, relationship of the appearance of periarteritis nodosa following the activation of his tuberculosis on several occasions would seem to make this a likely possibility. So far as is known, this is the only reported case in which the condition seems to be related to a tuberculous infection. Dr. S. Howard Armstrong said, in his discharge appraisal of this patient from the Peter Bent Brigham Hospital: "Although I have seen no reports of periarteritis in association with active tuberculosis, there is no reason why such an infection, in releasing foreign proteins, might not be as capable of producing this reaction as the various foreign proteins employed by Rich."

In the case of G. H., no basic condition was found with which the lesions of periarteritis nodosa could be associated.

Until more work has been done on the etiology of periarteritis nodosa, it must be assumed that the inciting factor is on the basis of an allergy and everything possible must be done in an effort to find the causative antigen.

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18. Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules Diagnoses Ante Mortem, Am. J. M. Sc. **190**:317 (Sept.) 1935.

PROGNOSIS

The prognosis of such a disease as periarteritis nodosa is most difficult to evaluate. In previous studies, the facts were largely based on postmortem examination. In few cases was the condition diagnosed before death unless there was renal involvement, and then it has been the tendency to predict for the disease an almost 100 per cent fatality rate. As there is more awareness of this illness, especially when the diagnosis is made in cases in which there is no asthma or renal involvement, the prognosis must be altered.

In the case of F. C., no evidence of renal involvement was present at any time, and from clinical study the only arteries involved were those supplying the peripheral muscles of the extremities and possibly the cerebral arteries. At the time when the condition was originally diagnosed it was felt that the outlook was hopeless and that his illness would soon prove fatal. However, after several months of rest in bed, which, in retrospect, probably arrested the activity of the cervical tuberculous adenitis and caused a cessation of the progress of the periarteritis nodosa, he was able to resume normal activities except at the times when the tuberculous adenitis was reactivated. It is my opinion that this patient will remain comparatively well as long as he restricts his activities to the level at which his cervical tuberculous adenitis remains quiescent. He is now alive and well six years after the original diagnosis was established. After a careful study of the literature, this is found to be the only definitely proved instance (along with those reported by Motley [19] and Fitz [20]) of a recovery which left the patient not only alive and well but able to practice his profession. Motley,[21] in a report of 2 cases in which the diagnosis was also made by biopsy of peripheral nodes, stated that 1 patient died suddenly of a coronary occlusion and the other [19] allegedly recovered entirely and was clinically well in 1944. Fitz and others [20] reported a case in which the disease was of unusually long duration, lasting from 1929 to 1935, a period of six years. The diagnosis was made by reexamination of the gallbladder and appendix, both of which had been removed previously. Fitz recalls the patient whom Parkhurst[22] reported on and who lived for six years after the diagnosis was made by nodular biopsy.

Although there are many cases in the literature in which longevity has been reported and in which the patients were apparently well for three or four years after the establishment of the diagnosis, personal

19. Motley, L.: Periarteritis Nodosa with a Report of a Case Showing Unusual Features and Apparent Recovery, J. A. M. A. **106**:898 (March 14) 1936.

20. Fitz, R.; Parks, H., and Branch, C. F.: Periarteritis Nodosa: Report of a Case, Arch. Int. Med. **64**:1133 (Dec.) 1939.

21. Motley, L.: Personal communication to the author.

22. Parkhurst, A. R.: Personal communication to the author.

attempts by correspondence to obtain further information have not met with success.

Weiss [23] stated that "it is probable that the prognosis will improve when the disease is oftener recognized clinically."

From a review of the literature and from personal experience, it seems apparent that when the disease involves the arteries of the lungs, kidneys or abdominal viscera the prognosis is grave. In the case of G. H., the arteries of the abdominal viscera and the coronary arteries were undoubtedly affected early in the illness, although no definite involvement of the renal arteries was apparent at this time. He had a temporary remission. However, his death within six months after the onset of symptoms was inevitable, and the observations at autopsy proved the widespread involvement of the arteries of the abdominal viscera, the heart and the kidneys.

In contrast, it is probable that many cases of periarteritis nodosa manifest themselves solely by involvement of peripheral arteries not supplying vital organs. The disease arrests itself spontaneously, or with the removal of a possible antigen the patient recovers. Thus, if the diagnosis is based solely on the biopsy of a peripheral nodule or muscle, without clinical manifestations of renal, pulmonary or abdominal involvement, the prognosis should be considered more favorable.

SUMMARY AND CONCLUSION

Two highly contrasting cases of periarteritis nodosa are described, both involving members of the Chinese race. Although the medical literature on the subject of this disease was thoroughly and carefully studied, there was no other mention found of a member of the Chinese race with periarteritis nodosa. But it is nevertheless interesting to note that in the twelve year period from 1935 to 1947 we have had under medical observation at Harvard University approximately 80,000 students and these two Chinese men were the only ones who had periarteritis nodosa in the entire student body. The number of Chinese students at Harvard University is small, making up only about 1 per cent of the total.

In 1 of the patients, F. C., the etiologic factor is assumed to have been a tuberculous antigen. This patient is apparently well and active six years after the establishment of the diagnosis by biopsy of a peripheral nodule. In the second patient, G. H., no evidence of allergy could be found, and although the diagnosis was strongly suggested it was not proved until the autopsy.

The symptomatology, diagnosis, etiologic factors and prognosis of periarteritis nodosa have been discussed.

23. Weiss, S.: Arteritis: Disease Associated with Inflammatory Lesions of the Peripheral Arteries, New England J. Med. **225**:579, 1941.

AMBULATORY MANAGEMENT OF AZOTEMIA AND CLINICAL UREMIA

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DURING a nine month period, 21 patients with azotemia and clinical uremia having serum creatinine concentrations of over 3 mg. and serum urea concentrations of over 80 mg. per hundred cubic centimeters were treated in the Clinic for Renal Disease of the Stanford University School of Medicine. Their illnesses varied in severity from azotemia without symptoms to frank clinical uremia. Most of these patients were in the terminal stage of glomerular nephritis. One patient had polycystic kidneys, and 1 had chronic uremia of obscure origin.

It has been our experience, which is in conformity with past experience gained in the Clinic, that such patients can be managed satisfactorily on an ambulatory basis until the final stages of renal failure. In addition, the irregular and unpredictable course of severe chronic renal insufficiency has impressed on us the fact that there is always some hope that the patient may continue to lead a useful life for some time.

DIETARY MANAGEMENT

The patients were maintained on a diet containing 0.5 Gm. of protein per kilogram of body weight per day. To this was added an amount equal to the protein lost in the urine. On each visit to the Clinic the figure for the latter was obtained from quantitative determinations of the urine protein by the precipitate method of Addis.[1]

The patients were taught how to estimate the protein content of their diets quantitatively and were given a simplified booklet of protein values for common foods based on household measures. They were advised to take no meat, fish or fowl and to avoid soups and gravies prepared from these items. This regimen permitted them to use their few grams of protein with more latitude for other foods. In addition,

From the Department of Medicine, Stanford University School of Medicine.

1. Addis, T.: Glomerular Nephritis, New York, The Macmillan Company, to be published.

there is some reason to believe that purines and nucleoproteins of animal origin are harmful to the kidneys.[2]

So as to insure an adequate consumption of vitamins and minerals, a daily increment of these necessary factors was prescribed in the form of a polyvitamin and polymineral preparation.

Whereas the strict limitation of salt consumption may be desirable in hypertension without uremia and may be essential in the degenerative stage of glomerular nephritis with edema, it may be dangerous in the presence of severe renal failure. Diminished tubular function depresses the reabsorption of sodium, and severe symptoms of sodium depletion may result if dietary restriction is excessive. The salt consumption, therefore, should not be reduced below 5 Gm. daily.

It is desirable to maintain high calory consumption, and this is done by the liberal use of fats and carbohydrates. Candy, cream, corn starch puddings and fruit juices fortified with lemon juice and sugar all provide sources of energy with little protein.

Fluid consumption should be maintained at a high enough level so that a large volume of dilute urine is produced, preferably about 3,000 cc. daily. Patients are encouraged to drink water and carbonated beverages at frequent intervals.

The value of reducing the dietary protein cannot be overestimated. Patients are frequently seen in the Clinic who have been on a high protein diet and are in severe clinical uremia, with drowsiness, muscular hyperexcitability, collapse and high serum urea and creatinine concentrations. Within a few days after institution of an adequate low protein diet the clinical condition improves, the serum urea concentration drops precipitously and the creatinine concentration may decline to a lesser degree. This effect in 10 patients is demonstrated in the accompanying table. The remaining patients in the series were not suitable for this demonstration since azotemia or clinical uremia developed while they were on adequate low protein diets as a result of progress in the renal lesion.

CASE 1.—C. P. is a 41 year old male drug clerk with known albuminuria and edema of the ankles since 1929. He was first seen in the Clinic on Dec. 19, 1946, for severe headache, dyspnea and hypertension of nine months' duration. He had been advised to take a high protein diet with much meat.

On the first visit the serum creatinine was 5.24 mg. and the serum urea was 163 mg. per hundred cubic centimeters. He had the urinary sediment of renal failure, with broad casts, and a remarkably high protein excretion of 26.2 Gm. in twenty-four hours. His weight was 76 Kg.

He was placed on a diet containing 20 Gm. of protein daily with no meat for one week and thereafter 55 Gm. of protein daily with 5 Gm. of salt and no limitation of calories. He was also given supplementary vitamins and minerals.

2. Newburgh, L. H., and Johnston, M. W.: High Nitrogen Diets and Renal Injury, J. Clin. Investigation **10**:153-160 (April) 1931.

At the end of the first week the serum creatinine level was unchanged, but the serum urea was 44.2 mg. per hundred cubic centimeters, and the twenty-four hour excretion of protein had dropped to 13.2 Gm. One month later the creatinine concentration had decreased markedly and the urinary protein excretion was only 7.7 Gm. in twenty-four hours. In addition, the urinary sediment showed a considerable diminution in the number of renal failure casts.

AMBULATORY CARE VERSUS HOSPITAL CARE

We have found that the long and unpredictable course makes it impractical to hospitalize the patients, except terminally and as a last

*Effect of an Adequate Low Protein Diet on Patients Whose Diet Had Not Been Restricted Previously.**

Patient	Date	Weight, Kg.	Daily Diet Protein, Gm.	Serum Urea, Mg. per 100 Cc.	Serum Creatinine, Mg. per 100 Cc.	Blood Pressure	Clinical Symptoms
H. O.	10/ 8/40	84.3	80	43	....	190/110	
	11/14/40	....	50	22	....	150/100	Subjectively improved
H. H.	1/25/45	83.2	Over 80	64	2.40	115/ 95	Edema, nausea and weakness
	2/15/45	....	45	46	....	115/ 95	Nausea and weakness diminished
L. L.	12/ 4/45	70.4	Over 80	83	....	155/105	
	12/11/45	....	45	59	....	145/ 80	No change
Y. Y.	4/ 2/46	76.2	Over 80	92	....	180/125	Considerable dyspnea and weakness
	4/13/46	....	55	67	....	180/110	Dyspnea and weakness much improved †
M. B.	4/ 9/46	66.4	Over 80	98	3.59	150/100	Felt well ‡
	4/20/46	....	40	46	2.90	140/ 96	
J. M.	9/28/46	63.1	Over 60	..	14.40	192/120	Nausea, weakness and exertional angina
	10/ 5/46	....	35	172	10.97	204/120	Nausea improved, other symptoms unchanged
B. C.	11/16/46	69.8	Over 80	136	4.71	210/160	Dyspnea on slight exertion
	12/ 7/46	....	40	38	4.71	148/ 82	Much improved †
C. P.	12/19/46	76.6	Over 80	163	5.24	200/135	Weakness and nausea
	1/ 2/47	....	55	58	4.71	170/130	Improved
V. M.	5/13/47	72.2	70	74	6.68	170/120	Weakness, nausea and twitching
	5/27/47	....	20 §	..	7.34	160/110	Dramatically improved
J. D.	5/29/47	68.2	80	101	6.75	184/130	Nausea, headache and weakness
	6/ 5/47	....	20 §	75	7.05	168/118	Subjectively improved

* The protein content of the diet before treatment was estimated from a diet survey.
† Digitalis was administered for cardiac failure.
‡ This patient had chronic uremia for which no cause had been found.
§ A very low protein diet was used for one week only, and the amount was then raised to 40 Gm. daily.

resort. They can be handled well as outpatients. They may be capable of leading relatively normal lives in spite of the presence of azotemia, anemia and associated symptoms of clinical uremia. One of our patients has been attending law school during a period when his serum creatinine has varied from 6 to 10 mg. per hundred cubic centimeters (case 3). Such persons are much happier when assisted to lead lives which, though activity is limited, are as normal as possible.

In general, the degree of activity permissible depends on the patient's own judgment. Weakness and dyspnea are the signals that advise him to reduce his activity.

At the end of the illness, hospitalization may of course become necessary to relieve nausea, muscular twitching, convulsions and other terminal events.

CONTROL OF ANEMIA

The progressive anemia which accompanies azotemia and which can almost be considered an index of the course at times becomes troublesome. There may be a critical level for the patient, below which he is uncomfortable. Because of diminished oxygen-carrying capacity of the blood when the hematocrit reading falls below this critical level, the patient may experience weakness, dyspnea and at times anginal pain. Such symptoms may be relieved rapidly by transfusion of whole blood or preferably of concentrated red cells. Since the latter preparation contains little protein in solution, it does not overload the circulation with a sudden increase in blood volume.

CASE 2.—F. G. was a 47 year old housewife who was found to have polycystic kidneys in 1932. She was followed in the Clinic from 1935 until her death in February 1947.

She was placed on a diet containing 40 Gm. of protein per day without meat. Her weight was about 52 Kg., and the urinary protein excretion was less than 1 Gm. in twenty-four hours. When she was first seen the serum urea concentration was 31.4 mg. per hundred cubic centimeters, the hematocrit reading was 38 mm. (Wintrobe) and her blood pressure was 210 systolic and 90 diastolic.

There was little change in her condition until 1941, after the uneventful birth of a child. From that time on the serum urea concentration slowly rose and the value for the hematocrit reading gradually declined. Her blood pressure remained unchanged. In October 1945 the hematocrit reading had fallen to 23 mm., the serum creatinine concentration was 10.97 mg. per hundred cubic centimeters and she complained of dyspnea, weakness and anginal pain on exertion. A loud diastolic murmur was heard along the left sternal border. She was given 4 pints (1,892 cc.) of whole blood, which relieved all her symptoms and returned the hematocrit reading to 38 mm.

She did not require transfusion again until November 1946 and again in January 1947. Each time the indications were a decrease in the hematocrit reading to 23 mm., with a return of dyspnea and exertional angina. Transfusions brought rapid relief.

There are persons, however, for whom the use of transfusions not only is of little avail but also may actually increase discomfort. In one case (case 3) transfusion was followed by a rapid return of the hematocrit reading to low levels. During the period of fall, the patient complained of increased weakness and dyspnea, which disappeared after the low level was stabilized.

ACIDOSIS

Patients in advanced renal failure tend to exhibit acidosis, which may become severe. Development of acidosis is due principally to two factors. The tubules fail in their ability to excrete sulfate and phosphate ions, so that these accumulate in the body. The tubules also fail in their ability to reabsorb sodium and to produce ammonia, which normally spares the fixed bases. Nausea and anorexia, with diminished fluid consumption, further aggravate the situation. Other factors may operate to a lesser degree.

In the practical management of uremia, acidosis should not be a problem until the last stages. If a large fluid consumption is maintained, with a copious flow of urine, and if enough salt is allowed in the diet to replace that lost in the urine, the homeostatic mechanisms of the body will maintain an adequate acid-base balance. In the last stages of uremia, when the patient loses his ability to drink and eat, acidosis may become difficult to control except through the parenteral administration of fluids.

SEDATION

Sedation is of use in the control of nausea, muscular hyperexcitability and convulsions. Paraldehyde has the disadvantages associated with its odor and with pulmonary excretion, but it is an ideal sedative in uremia. Its metabolism does not involve the kidney, and it is excreted rapidly. If barbiturates are used, it is essential to select those, such as sodium pentobarbital and "seconal sodium" (N.N.R.) which are short acting and are destroyed principally by the liver. It is necessary to watch closely for cumulative effects. When muscular twitchings and convulsions are the result of low serum calcium concentration, the intravenous administration of calcium salts may relieve symptoms for a short time.

DIARRHEA

Persons with pronounced retention of urea may suffer from severe watery diarrhea, which may contain blood. This may result from excretion of urea into the bowel. There urea-splitting organisms liberate ammonia, which is capable of greatly irritating the mucosa. Confirmation of this idea may be found in the fact that a change in the flora and in the reaction of the bowel through the use of Lactobacillus acidophilus preparations usually causes considerable improvement in the diarrhea. Patients should be cautioned that in the event of the development of diarrhea or nausea and vomiting medical aid to replenish the salt, restore fluid balance and combat acidosis should be sought immediately.

CARDIAC FAILURE

Patients presenting themselves with azotemia and clinical uremia may at the same time have the situation complicated by the presence of

cardiac failure. In contrast to the cardiac failure which is associated often with the initial stage of glomerular nephritis and is probably the result of a sudden increase in blood volume, the cardiac failure associated with uremia is usually the result of chronic hypertension, with left ventricular hypertrophy and insufficiency.

Cardiac failure in the presence of uremia should be treated by digitalization and by any other ordinarily indicated measures except the further limitation of salt consumption. With improvement in cardiac status, a parallel improvement in azotemia and renal clearances may result. This may be due to improved circulation to the kidney, with the relief of congestion in the renal veins.

PROGNOSIS

A definite prognosis cannot be offered to a patient with azotemia or uremia. In no medical condition may the end seem more inevitable. Yet the course may confound and amaze the physician. It is true that of the 21 patients observed during the past nine months 2 have died and the fate of 2 others, who when last seen were approaching the moribund condition, is uncertain. On the other hand, in 2 patients who have been followed for some time with elevated serum urea and creatinine levels progressing upward from visit to visit and with clinical symptoms of advanced uremia the process has suddenly reversed and the improvement is striking. The following case is illustrative.

CASE 3.—R. Y. is a 28 year old law student and retired naval officer. In October 1944 a routine physical examination revealed albumin, granular casts, leukocytes and red blood cells in his urine. He was studied in naval hospitals and told that he had chronic nephritis, for which he was retired. There was no knowledge of any initial episode, and previous examinations had failed to reveal abnormalities.

He was kept on a high protein diet until he came to the Clinic on April 2, 1946. He was found then to be in the terminal stage of glomerular nephritis. His blood pressure was 180 systolic and 125 diastolic, the serum urea 92.3 mg. per hundred cubic centimeters, the total serum protein 5.77 Gm. per hundred cubic centimeters and the hematocrit reading 28 mm. (Wintrobe). The specific gravity of the urine was 1.010, and he was excreting 10.5 Gm. of protein, 60,000,000 leukocytes and 630,000,000 erythrocytes in twenty-four hours. Few casts were seen. He weighed 76 Kg. There was moderate pitting edema, and the liver extended two fingerbreadths below the costal margin. His heart was enlarged, with regular rhythm and no murmurs.

He was digitalized and placed on a diet containing 55 Gm. of protein per day without meat, with no limit on calories and with salt restricted to 5 Gm. daily. He improved rapidly, with loss of edema and a drop of the serum urea to 48 mg. per hundred cubic centimeters. On May 4, 1946, the serum creatinine concentration was 2.96 mg. per hundred cubic centimeters.

He felt well enough to play golf and enroll as a law student with a full schedule, although he was counseled against overtaxing himself. The serum creatinine level rose steadily during the succeeding months, reaching 7.90 mg. on Jan. 4, 1947. At that time the serum urea was 125 mg. per hundred cubic centimeters,

the hematocrit reading was 23 mm. and the urinary sediment showed many broad casts of the type seen in renal failure. He felt weak and fatigued easily, and he entered the hospital for transfusions of whole blood and red cells.

Following the transfusions, he did not feel much better, although the hematocrit reading rose to 35 mm. His serum creatinine level rose to 9.88 mg., and the serum urea level was 143 mg. per hundred cubic centimeters. Watery diarrhea developed which was troublesome. The hematocrit reading rapidly dropped back to 23 mm. in one month.

On March 18 he was given transfusions of concentrated red cells and whole blood. The hematocrit reading responded promptly, but his subjective response was again poor. The diarrhea, however, was completely relieved by daily administration of a Lactobacillus preparation (yoghurt).

Because of the failure in subjective response to blood, the patient refused further transfusion. The hematocrit reading fell to 23 mm. again on May 6. He said that once it was stabilized at the low level he felt better and had more energy.

At this point there was a remarkable change in his course, and, with no change in treatment, he began to improve. Although the hematocrit reading was still only 24 mm. on June 3, his serum creatinine had fallen to 3.82 mg. per hundred cubic centimeters. The character of the renal sediment had altered completely, with appearance of oval fat bodies. The excretion of protein fell from levels of 10 to 15 Gm. to 2.6 Gm. in twenty-four hours. Excretion of erythrocytes fell from 1,545,000,000 to 18,000,000 in twenty-four hours, and the endogenous creatinine clearance rose from 12.7 to 23.7 per cent of normal. He feels much better and is pursuing his studies with renewed vigor.

COMMENT

There has been much debate in the past concerning the minimum amount of protein in the diet required to maintain health. At the time of Lusk's classic work the accepted figure was from 1.0 to 1.5 Gm. of protein per kilogram of body weight per day. Subsequently, Sherman [3] determined the requirement to be 0.5 Gm. per kilogram per day. Hegsted and others [4] confirmed that figure. In order to maintain the level safely above the minimum requirements, we have used 0.5 Gm. per kilogram per day, to which is added an amount equal to that lost in the urine.

Addis,[5] Newburgh [6] and Borsook and Winegarden [7] have stressed the fact that excretion of urea plays a preponderant role in determining

3. Sherman, H. C.; Gillett, L. H., and Osterberg, E.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, J. Biol. Chem. **41**:97-109 (Jan.) 1920.

4. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, J. Lab. & Clin. Med. **31**:261-284 (March) 1946.

5. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, Tr. A. Am. Physicians **4**:223-229, 1940; The Treatment of Chronic Renal Insufficiency, J. Urol. **41**:126-136 (Feb.) 1939.

6. Newburgh, J. D.: The Changes Which Alter Renal Osmotic Work, J. Clin. Investigation **22**:439-446 (May) 1943.

7. Borsook, H., and Winegarden, H. M.: The Work of the Kidney in the Production of Urine, Proc. Nat. Acad. Sc. **17**:3, 1931.

the osmotic work done by the kidneys in the secretion of urine. In view of the fact that protein in excess of anabolic needs is deaminized to form urea, it seems reasonable to suppose that protein in excess of that needed for the body economy will sharply increase the work of the kidneys.

Experimentally, this has been confirmed by Addis and others,[8] who studied the effect of dietary protein on rats from which three quarters of the kidney substance had been removed by operation. They found that a diet adequate but not excessive in protein maintained the rats in good health without nitrogen retention. However, increasing the dietary protein content by increments created and increased nitrogen retention, until, at the highest dietary levels, the rats died with steadily mounting azotemia and uremia.

Since osmotic work is a function of concentration gradients, the desirability of a large urine volume with relatively low concentrations of solutes seems self evident.

We believe that the management of uremia is best served by the positive measures proposed. With their use, life may be prolonged and the patient may be made comfortable to the maximum possible degree.

SUMMARY

Twenty-one patients with azotemia and clinical uremia have been studied during nine months.

A program of positive measures for management is offered, based on an adequate low protein diet and a high urine volume.

8. Addis, T.; Barrett, E.; Lew, W.; Poo, L. J., and Yuen, D. W.: Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue, Arch. Int. Med. **77**:254-259 (March) 1946.

VASCULAR RESPONSES IN MAN TO LIGATION OF THE INFERIOR VENA CAVA

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NEW ORLEANS

LIGATION of the inferior vena cava for phlebothrombosis and thrombophlebitis is not a new therapeutic procedure. The first ligation was performed by Kocher in 1883 and the second two years later by Billroth.[1] There have been few papers [2] on the subject until recently. Since publication of the article by Collins and others,[3] however, there have been a considerable number of reports.[4]

This procedure would seem drastic to most clinicians. Nevertheless, it has been used without apparent serious disturbances clinically. Since ligation of the inferior vena cava is being performed in greater numbers, it is imperative that certain physiologic observations be made to evaluate the circulatory adjustments. There have been fairly extensive observations on experimental animals [5] but relatively few in man. In fact,

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1. Plaff, O. G.: Ligation of the Inferior Vena Cava, Am. J. Obst. & Gynec. **11**:660-663, 1926.

2. Krotoski, J.: Zur Venenunterbindung bzw.-extirpation bei der puerperalen allgemeininfektion vom chirurgischen Standpunkt, Chirurg **9**:425-439, 1937; cited by Moses.[4c] Ochsner, A., and DeBakey, M.: Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis, New England J. Med. **225**:207-227, 1941.

3. Collins, C. G.; Jones, J. R., and Nelson, E. W.: Surgical Treatment of Pelvic Thrombophlebitis: Ligation of Inferior Vena Cava and Ovarian Veins; Preliminary Report, New Orleans M. & S. J. **95**:324-329, 1943.

4. (*a*) Gaston, E. A., and Folsom, H.: Ligation of the Inferior Vena Cava for the Prevention of Pulmonary Embolism, New England J. Med. **233**:229-233, 1945. (*b*) O'Neil, E. E.: Ligation of the Inferior Vena Cava in the Prevention and Treatment of Pulmonary Embolism, ibid. **232**:641-646, 1945. (*c*) Moses, W. R.: Ligation of the Inferior Vena Cava or Iliac Veins, ibid. **235**:1-7, 1946.

5. Polkey, H. J.: The Phenolsulphonephthalein Output After Ligation of the Vena Cava and Renal Veins, Urol. & Cutan. Rev. **33**:294-297, 1929. Whittenberger, J. L., and Huggins, C.: Ligation of Inferior Vena Cava, Arch. Surg. **41**:1334-1343 (Dec.) 1940.

there has been only one preliminary report [6] devoted to the study of vascular responses to ligation of the inferior vena cava. It is the purpose of this presentation to describe certain types of studies directed to clarify the circulatory readjustments in man precipitated by sudden occlusion of the inferior vena cava.

METHODS

These observations are limited to 12 patients, all women (table 1 indicates the variations in age and race), in whom the inferior vena cava had been ligated by Dr. C. G. Collins, of the Department of Gynecology and Obstetrics of the Tulane University of Louisiana School of Medicine, in the treatment of pelvic thrombophlebitis. The severity of the illness prevented the removal of the patients to our laboratory early after operation. As soon as the patients' postoperative condition permitted, they were moved to the laboratory with controlled atmospheric conditions. The observation room is quiet and draft free.

The patients were transported to the laboratory on a roller when they were not ambulatory. They rested for at least thirty minutes in a hospital-type bed before any observations were made. They removed all except their underclothing and were covered with a sheet to an extent necessary for comfort. The underclothing was loosened to prevent constriction and interference with the circulation. The duration of each period of observation did not exceed two hours, thus avoiding fatigue. There were no medications administered during the day of study, and observations were not begun until at least two hours after the patients had eaten.

The methods and details for each type of observation are discussed separately. Some of the patients have been observed for as long as four and one-half years.

VENOUS PRESSURE

The phlebomanometer [7] was used to determine the venous pressure. All determinations were carried out with the vein at the phlebostatic level.[8] The determinations were made in the dorsal venous arch of each foot, the superficial abdominal veins bilaterally and the antecubital vein unilaterally.

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6. Burch, G. E., and Winsor, T.: Physiological Studies on Five Patients Following Ligation of the Inferior Vena Cava, Proc. Soc. Exper. Biol. & Med. **53**:135-138. 1943.

7. Burch, G. E., and Winsor, T.: The Phlebomanometer: New Apparatus for Direct Measurement of Venous Pressure in Large and Small Veins, J. A. M. A. **123**:91-92 (Sept. 11) 1943.

8. Winsor, T., and Burch, G. E.: Phlebostatic Axis and Phlebostatic Level: Reference Levels for Venous Pressure Measurements in Man, Proc. Soc. Exper. Biol. & Med. **58**:165-169. 1945.

Results.—The results are are summarized in table 1. In only 1 instance was there no elevation in venous pressure following the operation (case 10). Initially, the venous pressures varied from 120 to over 600 mm. of water, or from 60 mm. below to over 425 mm. above the mean normal values.[9] There was a gradual decline in venous pressure

TABLE 1.—*Venous Pressure (Millimeters of Water) in Veins of the Extremities and Abdominal Wall of Twelve Patients with Ligation of the Inferior Vena Cava*

				Vein					
					Dorsal Pedal				
Case	Age, Yr.	Race	Date of Measurement	Antecubital	Right Foot	Left Foot	Right Abdominal	Left Abdominal	Date of Operation
1	21	W	4/11/42	122	...	248	...	...	3/19/42
2	31	N	5/20/42	...	360	500+	...	...	5/ 2/42
			6/24/42	106	356	366	...	...	
3	21	W	5/22/42	110	416	506	...	...	4/30/42
			3/ 9/43	140	200	220	...	...	
			3/ 6/46	120	320	330	...	...	
			10/18/46	120	300	280	...	202	
4	67	W	4/20/42	26	...	244	...	...	3/28/42
			6/30/42	106	...	306	...	...	
			11/ 7/42	50	300	300	...	...	
			2/12/46	120	210	210	...	...	
5	27	W	4/28/42	112	...	320	...	...	4/25/42
			5/ 7/42	140	...	290	...	...	
			6/ 1/42	126	...	256	...	...	
			11/10/42	100	170	180	...	...	
			3/20/46	120	200	190	...	...	
			10/15/46	140	180	185	...	...	
6	34	W	2/27/46	130	330	330	..	..	6/14/42
			10/21/46	128	322	314	60	80	
7	45	N	2/20/46	120	420	340	...	...	2/ 5/46
			4/29/46	110	314	280	...	...	
			6/13/46	120	280	280	...	...	
			8/12/46	90	420	340	...	...	
			10/15/46	110	420	360	170	170	
8	22	N	2/ 6/46	100	462	600+	...	...	12/21/45
			5/ 2/46	100	480	600+	...	...	
			10/15/46	120	430	320	140	120	
9	26	W	5/25/46	120	300	320	...	...	5/25/46
			10/18/46	120	306	240	...	254	
10	27	N	4/ 3/46	110	120	120	...	...	3/20/46
			5/11/46	80	120	120	...	...	
11	43	N	10/18/46	110	316	320	...	220	6/26/46
12	36	N	6/13/46	100	220	200	...	...	6/13/46
			6/15/46	100	300	250	...	...	
Mean				110	306	302	123	174	
Maximum				140	480	600+	170	254	
Minimum				26	120	120	60	80	

toward normal, but it returned to within the maximum limits of normal in only 2 instances (cases 4 and 5). The average decline in four years was 69 mm. of water in the right foot and 135 mm. in the left. The

9. Winsor, T., and Burch, G. E.: Use of the Phlebomanometer: Normal Venous Pressure Values and a Study of Certain Clinical Aspects of Venous Hypertension in Man, Am. Heart J. **31**:387-406, 1946.

mean pressure four years after ligation was 253 mm. of water in the right foot and 247 mm. in the left, whereas the mean values for all initial determinations were 337 mm. in the right foot and 342 mm. in the left. In the patients followed for shorter periods there was a decline in the venous pressure in most instances. In some subjects the venous pressure fell and then rose to or above the initial value; at times the rise was followed by a second decline.

The venous pressure in the antecubital veins remained within normal limits. The low value of 26 mm. of water in case 4 is probably due to an error.

The venous pressure in the superficial abdominal veins was determined in 6 patients. In 1 the values were within normal limits (case 6), while in the other 5 the pressures were markedly elevated (table 1), reaching 254 mm. of water in 1 instance (normal values, 80 to 110 mm. of water).

Comments.—From the venous pressures obtained it is obvious that the degree of effective venous obstruction resulting from ligation of the inferior vena cava is variable. For example, in case 8 the venous pressure in the dorsal vein of the left foot was greater than 600 mm. of water, while in case 10 it was within normal limits. Such a variation indicates either a good venous collateral return in the patient in case 10 and a poor return in the patient in case 8 or incomplete ligation in the former. However, autopsy revealed a complete ligation in the patient with a normal pressure. The notable variations in local venous hypertension following ligation are most probably the result of variations in collateral venous circulation. This concept is further supported by the fact that the venous pressure in the left foot of the patient in case 8 was greater than 600 mm. of water while at the same time it was 462 mm. in the right foot. Such a difference cannot be due to incomplete ligation of the vena cava. The same sort of bilateral variations is well illustrated in case 2. The reasons for these differences in collateral circulation remain unknown. Such factors as duration and extent of the thromboses and inflammation must be of some importance. Section of the lumbar sympathetic nerves did not influence the venous pressure.

The paucity or even absence of edema (tables 1 and 6) in the lower extremities even with considerable elevations in venous pressure makes it necessary to reevaluate the role of hydrostatic pressure in edema formation. This is particularly true in congestive heart failure, in which the elevation in venous pressure is usually relatively small and the degree of edema pronounced. It is well to note that patients who had edema immediately after ligation became clinically free of it in the presence of continued extreme venous hypertension and even when

they maintained an erect posture throughout the day. The degree of the edema and the height of the venous pressure were not proportional in these patients. Such findings indicate the efficient compensatory mechanisms concerned locally with water balance in tissues.

An interesting factor was the absence of abnormal dilatation of the veins of the legs and the feet even in the presence of pronounced venous hypertension. In fact, in some instances the veins were smaller than normal, indicating severe venous spasm. Biopsy of veins from the foot of a patient (case 9) showed a "functional phlebomesohyperplasia" (details to be described elsewhere). This is probably the result of continuous venous "spasm" over many months.

The definite venous hypertension in the superficial low abdominal veins in 5 of 6 patients studied indicates the development of venous collateral flow through these veins. In every instance the direction of blood flow was cephalad instead of caudad.

PLETHYSMOGRAMS

A quantitative study of the variations in volume of the tips of the fingers and toes was performed plethysmographically.[10] All values recorded by the plethysmograph are expressed in cubic millimeters of volume change per 5 cc. of part. The volume changes in response to general environmental cold (room temperature 63 F. and relative humidity 55 per cent) and heat (temperature 110 F. and humidity 55 per cent) were recorded in addition to the volume changes in a comfortable room atmosphere (temperature 78 F. and relative humidity 55 per cent). The right index finger was observed as a control. The effect of the psyche on vascular responses was reduced to a minimum by the avoidance of noises, the removal of the plethysmograph and other equipment to an adjoining room and the use of a specially constructed room for the subject.[11]

Section of the lumbar sympathetic nerves[12] was not performed in cases 1 to 6 inclusive. The operation was confined to the right side in cases 7 and 10.

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10. Burch, G. E.: A New Sensitive Portable Plethysmograph, Am. Heart J. **33**:48-75, 1947.

11. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects, J. Clin. Investigation **21**:651-654, 1942.

12. Section of the lumbar sympathetic nerves performed at the time the vena cava was ligated consisted of sectioning the lumbar sympathetic chain at the level of the fourth lumbar vertebra.

Results.—The results are summarized in table 2. In the main, there was a tendency for the volume of the pulse and alpha deflections to be small immediately after ligation. This increased in magnitude as time progressed (table 2). Initially, the volume of the pulse deflections in

TABLE 2.—*Volume of the Pulse Deflections (cu. mm. per 0.4 cc. of Part) in the Tips of the Finger and Toes in Eleven Patients Following Ligation of the Inferior Vena Cava*

		Right Index Finger			Right Second Toe			Left Second Toe		
Case	Date	CT*	C*	H*	CT*	C*	H*	CT*	C*	H*
1	4/11/42	3.5	...	...	0.3	...	...	...	...	...
2	5/20/42	4.0	...	...	0.5	...	...	...	...	...
	6/24/42	11.0	...	...	1.2	...	...	...	...	...
3	5/22/42	6.9	...	...	3.5	...	...	...	...	...
	3/ 9/43	2.1	...	...	0.8	...	...	...	...	...
	3/ 6/46	2.5	1.0	4.0	0.8	0.4	3.1	0.5	0.3	3.1
	10/18/46	7.3	...	...	3.4	...	...	2.1	...	...
4	4/20/42	8.9	...	...	1.2	...	...	...	...	...
	6/30/42	10.3	...	...	2.7	...	...	...	...	...
	11/ 7/42	10.1	...	...	...	...	...	...	...	...
	2/12/46	7.0	...	...	3.0	...	...	3.1	...	...
5	5/ 7/42	4.1	...	...	0.4	...	...	...	...	...
	6/ 1/42	7.5	...	...	6.0	...	...	...	...	...
	11/10/42	9.9	...	...	5.6	...	...	...	...	...
	3/20/46	6.4	0.9	7.3	5.2	2.1	8.3	5.2	2.1	8.3
	10/15/46	2.1	...	...	2.2	...	...	2.2	...	...
6	2/27/46	6.4	2.1	10.0	3.3	1.5	4.5	3.3	1.5	4.5
	10/21/46	10.0	...	...	5.2	...	...	4.6	...	...
Mean		6.7	1.3	7.1	2.7	1.4	5.3	3.0	1.3	5.3
Maximum		11.0	2.1	10.0	6.0	2.1	8.3	5.2	2.1	8.3
Minimum		2.1	0.9	4.0	0.3	0.4	3.1	0.5	0.3	3.1
7	2/20/46	2.1	0.6	6.6	2.7	2.2	2.2	1.1†	0.2†	2.2†
	4/29/46	5.5	...	5.5	3.9	...	3.7	0.9†	...	3.7†
	6/12/46	3.1	...	...	1.3	...	...	0.5†	...	...
	10/15/46	3.0	...	...	1.0	...	...	0.5†	...	...
8	2/ 6/46	2.5	...	6.2	2.7	...	2.6	2.7	...	3.3
	5/ 2/46	6.2	...	...	5.3	...	...	6.6	...	...
	10/15/46	5.8	...	...	1.9	...	...	...	...	...
9	5/25/46	2.8	...	...	2.1	...	...	2.1	...	...
	6/ 3/46	3.1	...	...	3.5	...	...	2.8	...	...
	10/18/46	6.8	...	...	4.2	...	...	5.0	...	...
10	4/ 3/46	4.4	...	...	8.3	...	...	0.1†	...	...
	4/10/46	1.4	...	...	5.6	...	...	3.5†	...	...
	5/11/46	0.3	...	...	0	...	...	0.7	...	...
11	10/18/46	4.3	...	...	3.2	...	...	3.2	...	...
Mean		3.7	0.6	6.1	3.5	2.2	2.8	3.9	...	3.3
Maximum		6.8	...	6.6	8.3	...	3.7	6.6	...	...
Minimum		1.4	...	5.5	1.0	...	2.2	2.1	...	...
Mean								1.1†	0.2†	2.9†
Maximum								3.5†	...	3.7†
Minimum								0.1†	...	2.2†

* CT indicates comfortable room atmosphere; C, cool room atmosphere, and H, hot room atmosphere.

† These values were obtained in the extremity with a unilaterally intact sympathetic nervous system (consult text).

the toe tips was reduced to a mean value of 1.2 cu. mm. per 5 cc. of part in the patients with an intact sympathetic innervation. This value increased over a period (up to four years) to mean values of 2.7 cu. mm. for the tip of the right toe and 3.0 cu. mm. for the tip of the left. These

were still below the normal mean.[13] The mean volumes of the pulse deflections in the patients who underwent section of the sympathetic nerves were 3.5 cu. mm. for the right toe and 3.9 cu. mm. for the left, with maximums of 8.3 and 6.6 respectively. These values compare favorably with the normal. Ligation of the inferior vena cava modified by section of the lumbar sympathetic nerves resulted in a greater magnitude of the pulse deflections. The tip of the left toe of the patients in cases 7 and 10, in whom section of the right lumbar sympathetic nerves was performed, showed markedly diminished pulse deflections, the mean value being 1.1 and the maximum 3.5 cu. mm. It is important to note that the volume of the pulse deflections was increased by heat in the toes of patients with intact sympathetic innervation and reduced by heat in the toes of those subjected to section of the ipsolateral lumbar sympathetic nerves.

All patients had normal pulse deflections in the finger tips. The reactions to cold (vasoconstriction) and to heat (vasodilatation) were normal. The patients on whom section of the lumbar sympathetic nerves was performed had a volume of the pulse deflections in the finger tips which was less than normal but reacted normally to heat.

In case 10 there was occlusion of the right anterior tibial artery by an arterial embolus before the last tracing was made. There were no measurable volume deflections in the tip of the right second toe except for gamma deflections of small magnitude.

Comment.—The mechanisms for the decrease in the volume of the pulse and alpha deflections immediately following ligation are unknown. Previous studies [14] indicated that the influence of venous pressure per se resulted in marked distention limiting further distensibility of the peripheral vessels. This is an important contributing factor which reduces the volume of the deflections. The fact that section of the unilateral sympathetic nerves resulted in ipsolateral increase in the volume of the pulse deflections indicates arteriolar spasm and vasoconstriction in other vessels under sympathetic control as another important factor concerned with the small pulse deflections following

13. The normal value for the volume of pulsation of the finger tip is 6.9 cu. mm., with a maximum of 12.4 and a minimum of 2.1, and for that of the toe tip the mean value is 4.0 cu. mm., with a maximum of 11.5 and a minimum of 0.7. (Burch, G. E.; Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Resting Normal White Adults, Am. J. Physiol. **136**:443-447, 1942).

14. Burch, G. E.; DeBakey, M., and Sodeman, W. A.: Effect of Venous Pressure on Volume Pulsation, Proc. Soc. Exper. Biol. & Med. **42**:858-861, 1939. DeBakey, M.; Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, ibid. **41**:585-590, 1939.

ligation of the inferior vena cava. With the passage of time, there is a tendency for the volume deflections to return to within the normal range in spite of the fact that the venous hypertension persists. This suggests a decrease in vasoconstrictor tone in subjects with an intact sympathetic innervation.

The data were insufficient to test adequately for a correlation of the volume of the pulse deflections to the degree of edema, the degree of venous hypertension and the state of the sympathetic innervation.

The fact that the magnitude of pulse deflections decreased further when the room atmosphere was made cool and increased when the atmosphere was made hot indicated continued sympathetic and vasoconstrictor control of the peripheral blood vessels in the presence of obstruction of the vena cava and considerable venous hypertension. These responses were altered by section of the lumbar sympathetic nerves (table 2).

The embolic occlusion of the right anterior tibial artery of the patient in case 10 resulted in a disappearance of the pulse and alpha deflections in the right second toe. The slow but persistent gamma deflections indicated slow but definite shifting of blood in and out of the parts supplied by that artery. These shifts were probably of great significance in the maintenance of tissue nutrition, because there was only a superficial loss of tissue. The quantitative nature and significance of these shifts have not been fully evaluated. Their importance should be borne in mind.

RATE OF WATER LOSS

The rate of water loss from the right index finger tip, right second toe tip, right pretibial area and the volar surface of the right forearm was measured quantitatively by a method previously described.[15] The rate of water loss was determined for two successive fifteen minute periods, with an environmental temperature of 75 F. plus or minus 1 and a relative humidity of 50 per cent plus or minus 3. The room temperature was raised to 100 F. plus or minus 1 and the humidity to 75 per cent plus or minus 2 and measurements made for another two successive fifteen minute intervals. The rate of water loss was determined for 5 patients (cases 1 to 5).

Results.—The results shown in table 3 were previously described.[6] The normal values for the rate of water loss had been established previously.[16] There were no significant disturbances in water loss in a

15. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas with Results for Finger Tip, Toe Tip, and Postero-Superior Portion of the Pinna of Normal Resting Adults, Am. J. Physiol. **132**:748-756, 1941.

16. Burch, G. E., and Sodeman, W. A.: Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, Am. J. Physiol. **138**: 603-609, 1943.

comfortable environment or in a hot and humid one, the rate of water loss increasing under the latter conditions.

Comment.—The lack of disturbances in water loss in the comfortable environment shows that the circulatory disturbances associated with ligation of the vena cava do not greatly influence the diffusion of water through the skin of the legs. Likewise, the sweat function associated with thermal regulation is not changed materially, if at all, by ligation of the vena cava. These factors further indicate the relatively unimportant role played by hydrostatic intravascular pressure per se on the rate of diffusion of water through the skin or on the volume of sweat produced during periods of acute thermal regulation. They have even greater

TABLE 3.—*Rate of Water Loss (cu. mm. per 15 Minutes per 10 sq. cm. of Surface Area) Through the Skin of Five Patients Following Ligation of the Inferior Vena Cava*

Case	Date of Measurement	Right Index Finger		Right Second Toe		Right Leg		Right Forearm	
		CT *	HH *	CT *	HH *	CT *	HH *	CT *	HH *
1	4/11/42	50.2	149.0	18.8	39.5	....	....	11.2	63.0
2	5/20/42	21.6	98.7	7.7	30.1	11.0	30.6	....	....
	6/24/42	15.6	60.0	10.2	25.2	10.0	31.2	....	....
3	5/22/42	16.5	30.8	13.0	16.9	....	....	9.8	16.0
	3/ 9/43	20.7	53.5	9.8	23.7	....	....	4.6	12.6
4	5/20/42	15,5	27.7	6.9	19.5	18.0	38.2	....	....
	6/30/42	17.4	31.8	6.1	12.8	6.6	28.0	....	....
	11/ 7/42	24.7	28.0	13.5	17.6	10.0	27.2	....	....
5	6/ 1/42	13.7	24.5	12.1	19.3	....	....	10.8	23.6
	11/10/42	21.7	56.3	12.3	30.9	....	....	13.6	29.8
Mean		21.8	56.9	11.0	23.6	11.1	31.4	10.0	29.0
Maximum		50	149.0	18.8	39.5	18.0	38.2	13.6	63.0
Minimum		15.5	27.7	6.1	16.9	6.6	27.2	4.6	12.6
		Normal Values							
Mean		23.2	47.9	12.5	31.1	8.3	32.1	4.4	25.9
Maximum		41.3	52.1	15.7	48.7	13.6	37.6	8.4	37.8
Minimum		14.0	21.7	10.4	21.8	4.1	22.4	2.0	14.0

* CT indicates comfortable room temperature and humidity and HH hot and humid room temperature.

significance when compared with the decided reduction in the rate of sweating noted previously [17] in chronic congestive heart failure.

PLASMA PROTEIN

The plasma protein content was determined in 7 patients at varying intervals after ligation.

Results.—The results are summarized in table 4. There was a tendency for the plasma protein content to increase after ligation of the

17. Burch, G. E.: The Rate of Water Loss from the Skin of Patients in Congestive Heart Failure in a Subtropical Climate, Am. J. M. Sc. **211**:181-188, 1946.

vena cava. Although a rise did not occur in 3 of the 7 patients, relatively high values were reached in 2. The patient in case 3, with a total plasma protein level of 5.6 Gm. per hundred cubic centimeters, had persistent vomiting for four months, with a loss of 28 pounds (12.7 Kg.) in body weight. The patient in case 5 likewise had repeated vomiting for two months prior to the last determination. The patient in case 7 was on a self-imposed carbohydrate reduction diet for two months before Oct. 15, 1946.

Comment.—The significance of the tendency toward hyperproteinemia following ligation can only be conjectured. The relatively small number of patients studied makes the importance of the findings difficult to interpret. It is possible, however, that body mechanisms are so disturbed by the venous ligation that hyperproteinemia might be expected to

TABLE 4.—*The Plasma Protein Content (Grams per Hundred Cubic Centimeters) in Seven Patients Following Ligation of the Inferior Vena Cava*

Case	Date	Albumin	Globulin	Total
3	10/18/46	4.3	1.3	5.6
5	3/20/46	6.9	3.7	10.6
	10/15/46	4.1	2.3	6.4
6	10/21/46	5.9	1.8	7.7
7	4/29/46	5.1	3.2	8.3
	6/13/46	3.3	3.4	6.7
	8/12/46	4.8	3.5	8.3
	10/15/46	3.3	2.0	5.3
8	5/ 2/46	4.3	3.4	7.7
	10/15/46	4.4	2.3	6.7
9	10/18/46	6.7	2.7	9.4
11	10/18/46	3.9	1.9	5.8
Mean		4.8	2.6	7.4
Maximum		6.9	3.7	10.6
Minimum		3.3	1.3	5.3

result. The hyperproteinemia could be an important factor in limiting the degree of edema formation through its influence on intravascular oncotic force. More data are necessary to support claims that such adjustments are compensatory.

TISSUE PRESSURE

Measurements of the pressure in the subcutaneous tissue in the pretibial area were made in 6 patients at varying intervals after ligation by a direct method previously described.[18] All measurements were done with the part at heart level.

Results.—The results are shown in table 5. The normal value for tissue pressure in the volar surface of the forearm is 23.6 mm. of water

18. Burch, G. E., and Sodeman, W. A.: The Estimation of Subcutaneous Tissue Pressure by a Direct Method, J. Clin. Investigation **16**:845-850, 1937.

as a mean, with a maximum of 40 and a minimum of 11. For the pretibial area the mean value is 37.1 mm., the range being between 54 and 18.[18] In the only determination made on the volar surface of the forearm the value was found to be normal. In the pretibial areas the mean values were found to be 42 and 50 mm. of water for the right and left sides respectively. These mean values are at the maximum limit of normal for the pretibial area, thus indicating a rise in tissue pressure following ligation of the vena cava. There was a tendency for the magnitude of the tissue pressure in the pretibial areas to vary directly with the degree of the venous hypertension. The level of the tissue pressure varied inversely with the degree of edema in the lower extremities.

Comment.—The elevation of tissue pressure following ligation indicates the role of hydrostatic pressure of the tissues in limiting edema formation. The relative significance of this factor among the many

TABLE 5.—*Subcutaneous Tissue Pressure (Millimeters of Water) in Six Patients Following Ligation of the Inferior Vena Cava*

Case	Date	Arm	Right Leg	Left Leg
3	10/18/46	..	46	40
5	5/ 7/42	26	..	86
	10/15/46	..	28	28
7	10/15/46	..	30	45
8	10/15/46	..	58	58
9	10/18/46	..	58	56
11	10/18/46	..	30	36
Mean		26	42	50
Maximum		..	58	86
Minimum		..	28	28

other factors concerned with edema formation is not known. Previous studies [18] have indicated the importance of tissue pressure in edema formation, in which the former became progressively more significant as edema increased in magnitude.

CLINICAL OBSERVATIONS

Clinical observations consisted of the elicitation of a thorough history and physical and laboratory examinations, with frequent follow-up examinations in the postoperative period. Only pertinent findings are reported.

A. *Functional Capacity of Lower Extremities.*—There was no diminution in functional capacity either generally or locally. All the patients were able to do their usual duties without discomfort of any sort. There was no claudication.

B. *Edema.*—The results of the observations on edema are summarized in table 6. Edema was present in all patients except 2 (cases 9

and 10), in whom there was no edema either before or after the operation. The severity of the edema varied from mild to extreme among the 10 patients. It disappeared within two months after operation except in 3 patients. In several instances there was no clinical edema by the end of the third week. This disappearance of the edema occurred without a concomitant fall in venous pressure (tables 1 and 6). In only 2 patients did the edema persist for as long as eight months (cases 4 and 7). In case 4 the nature and behavior of the edema could not be properly evaluated since it was complicated by congestive heart failure during convalescence. Section of the sympathetic nerves had no influence on the occurrence, degree or disappearance of the edema.

C. *Skin.*—The temperature of the skin was noted by palpation and in a few instances by means of thermocouples. It remained within normal

TABLE 6.—*State of Edema in Twelve Patients Following Ligation of the Inferior Vena Cava*

Case	Course of Edema
1	Mild degree of edema in both legs for three weeks postoperatively; no edema after three weeks
2	Marked edema in both legs for several weeks; little edema eight weeks after operation
3	Edema severe in the right leg and moderate in the left for three weeks after operation; further observations revealed no edema
4	Considerable edema bilaterally for eight months after operation and then edema disappeared; congestive heart failure developed during convalescence
5	Slight bilateral edema two weeks after operation; no edema four weeks postoperatively or since that time
6	Edema more pronounced in the left leg; at the end of six weeks all edema was gone, and it has not appeared since that time
7	Edema of the left leg before operation; postoperatively, both legs were extremely edematous and at the last observation, eight months postoperatively, there was moderate edema of both legs
8	Slight edema for two months and none thereafter
9	No edema at any time
10	No edema at any time
11	Moderate edema at the last observation, four months after operation
12	Slight edema on the second postoperative day; patient died early after operation

limits. In the 2 patients in whom section of the unilateral sympathetic nerves was performed (cases 7 and 10) the leg on which partial sympathectomy had been performed was warmer than the opposite one.

D. *Nails.*—The toe nails did not change in rate of growth or in appearance after ligation of the inferior vena cava.

E. *Veins.*—The large veins of the legs and feet were not dilated. Indeed, one was impressed by the fact that the veins were smaller than would be expected normally. There were some small varicosities of the small veins of the skin, with an occasional rupture, in 4 patients. The extent of the varicosities was slight in 2, moderate in 1 and severe in another. However, there were no demonstrable varicosities in the large superficial veins of the lower extremities. The superficial veins of the abdominal wall and gluteal region and also the long thoracic vein

were dilated and formed an unusually prominant network. In a few instances the superficial abdominal veins were moderately tortuous. The direction of blood flow was invariably cephalad in these veins of the trunk.

F. *Miscellaneous.*—The skin of the legs and feet presented no abnormal pigmentation, cyanosis, mottling or discoloration of any sort. There was no change in the texture or thickness of the skin. Sensation to heat, cold, touch and pain remain undisturbed. There were no ulcerations or infections of the skin.

Comment.—The fact that the extremities failed to reveal clinically any change in function or in character of the skin or any discoloration, anatomic changes in the veins or neurologic dysfunction certainly indicates the adequacy of the compensatory readjustments following ligation of the inferior vena cava.

GENERAL COMMENT

The rather remarkable circulatory readjustments which occurred in the lower extremities of patients studied after ligation of the inferior vena cava are of considerable clinical importance. It is because of such adjustments that the surgeon can ligate the inferior vena cava, with the resultant sustained venous hypertension, without producing demonstrable detrimental effect. Needless to say, the ligation must be below the entrance of the renal veins. One of the most interesting adjustments is that concerned with the exchange of water between the intravascular and extravascular spaces. The fact that edema does not develop at all or develops to only a slight extent indicates the relatively unimportant role of hydrostatic intravascular pressure per se in edema formation. As long as only the hydrostatic pressure is increased, compensatory mechanisms develop to a high degree. It is such compensatory mechanisms which remain unknown and which deserve considerable study. The failure of edema to develop in the presence of a venous pressure of 400 mm. of water or more must cast doubt on the concepts presented to explain the edema in congestive heart failure on the basis of increased hydrostatic pressure.

The development of collateral circulation can be rapid and efficient. In 1 patient the pressures in the veins of the feet were normal soon after complete ligation of the inferior vena cava. This collateral circulation must be developed through the abdominal, gluteal, retroperitoneal, pelvic and hemorrhoidal veins.

The development of collateral circulation in these veins has been discussed by O'Neil.[4b] The ovarian veins are not concerned with collateral circulation in the patients reported on here since they were ligated along with the vena cava. The lymphatic system must play an

important part in limiting edema formation. Follow-up studies of the patients for as long as four and one-half years in some instances failed to reveal any clinical benefits from section of the sympathetic nerves. There was no difference in edema formation when section of the sympathetic nerves was performed and when it was not performed. The differences observed were limited to warmer extremities on the side subjected to section of the sympathetic nerves as well as the presence of greater volumes of the pulse deflections. In spite of this no evidence of over-all clinical benefit could be detected. It is possible that in certain circumstances, not observed in any of these cases, section of the sympathetic nerves might be advantageous.

SUMMARY AND CONCLUSIONS

Twelve female patients in whom the inferior vena cava was ligated for pelvic thrombophlebitis were studied for a period of up to four and one-half years. The methods of investigation were described and the results correlated with the clinical state of the patient.

After ligation of the inferior vena cava the pressure in the dorsal pedal veins was markedly elevated in all but 1 patient; the values ranged from 120 to over 600 mm. of water. A gradual fall in venous pressure occurred with time, but the maximum normal limits were reached in only 2 instances. There was no relation of venous pressure to the degree of edema or to section of the sympathetic nerves. The pressures in the antecubital veins were normal. Five of 6 patients studied had an elevated venous pressure in the superficial abdominal veins; values ranged from 60 to 254 mm. of water.

The volume of pulse deflections in the toe tips was reduced immediately after operation to a mean value of 1.2 cu. mm. per 5 cc. of part, which increased with time to mean values of 2.7 and 3.0 cu. mm. Section of the sympathetic nerves resulted in a greater mean value (3.5 cu. mm.) immediately after operation.

Five patients had a normal rate of water loss from the finger tips, volar surface of the forearm, pretibial area and toe tip in a comfortable environment, and the rate increased normally in response to a hot and humid environment.

The plasma protein levels tend to be slightly higher than normal, with mean values of 4.8 Gm. of albumin, 2.6 Gm. of globulin and 7.4 Gm. of total protein per hundred cubic centimeters. The range for total protein was 5.3 to 10.6 Gm., for albumin 3.3 to 6.9 Gm. and for globulin 1.3 to 3.7 Gm.

After ligation of the inferior vena cava, tissue pressure in the pretibial areas bilaterally rose to mean values of 42 and 50 mm. of water respectively. Tissue pressure tended to vary directly with the venous pressure and inversely with the degree of the edema.

Clinical observations revealed normal function of the lower extremities and normal texture, temperature, color and response to sensation of the skin. The veins of the feet and legs were small; varicosities were limited to minute veins of the skin. The abdominal veins were dilated, and the blood flow was cephalad. Edema occurred in all but 2 patients and disappeared early in convalescence in all except 2 in whom the edema was present for eight months.

Clinical and physiologic observations failed to reveal any deterimental effect from ligation of the inferior vena cava. The circulatory adjustments were adequate, although not all the compensatory mechanisms are clearly understood.

THROMBOSIS OF THE HEPATIC VEINS

The Budd-Chiari Syndrome

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IT IS THE purpose of this paper to report 2 cases of thrombosis of hepatic veins and review 95 from over 100 in the literature, to emphasize that the syndrome is not always due to one disease process, as is so commonly implied, and to attempt to give a clearer conception of the various other processes which may cause it.

In the majority of reported cases there is gross obstruction of hepatic veins, leading to engorgement and necrosis of the liver and to portal obstruction. In some instances the block occurs as a final episode in an already advanced disease which itself masks the characteristic clinical picture of the Chiari syndrome or leaves no time for its development. There is also a smaller group of cases in which the obstruction is limited to one lobe or to part of a lobe. While there is a pathologic unity which may be expressed by referring to all cases as examples of thrombosis of the hepatic veins, it is felt that descriptive separation is necessary. It is proposed that the name "Chiari" or "Budd-Chiari" syndrome should be retained for cases in which there is gross blockage of the hepatic veins and that cases with more limited lesions, not giving the full picture, should be referred to simply as cases of thrombosis of the hepatic veins. While this paper is primarily concerned with the Chiari syndrome, remarks concerning etiology and pathology cover the minor group also. Two previously accepted cases have been excluded. The patient in Sternberg's second case had thrombosis of the vena cava, but the upper part of the vessel was free, as apparently were the hepatic veins; reference is made only to a fatty liver. In Hoover's second case the diagnosis appears doubtful, and there was no autopsy.

Some reviews deserve special mention. These are the original paper by Chiari, an excellent review of the older literature by Hess, the paper by Thompson and Turnbull, the comprehensive article by Nishikawa containing a report of 10 cases and, more recently, the articles of Satke and Coronini and Oberson.

From the Royal Victoria Infirmary.

PATHOLOGY

Here will be described the pathologic processes leading to obstruction of the hepatic veins and the resulting hepatic changes.

Venous Lesions.—There are three main sites for obstruction. It may occur in the inferior vena cava, in the ostiums of the hepatic veins or in the hepatic veins themselves. It is often difficult to determine whether the thrombosis occurred primarily in the vena cava or in the ostiums of the hepatic veins. In 5 cases the block was due to neoplasm in the cava; in 2 of these the condition was reported as endothelioma (Hallock and others and Unruh) and in 3 as hypernephroma (Armstrong and Carnes; Jacobson and Goodpasture, and Weber). In 20 cases there was thrombosis of the cava—a rare lesion. Block of the upper part is extremely rare. Only 3 to 4 per cent of Pleasants' patients with thrombosis of the inferior vena cava had a thrombus in the upper third of the vessel. In 18 other cases there was mural thrombosis or intimal thickening without block.

In many cases the ostiums of the hepatic veins appear to be the initial site of the block; even when there is extensive thrombosis, scarring is frequently most severe and evidently of longer duration at this site. There remain a number of cases in which the ostiums are free, the most profound changes being in the hepatic veins themselves. Recently, authors have stressed lesions in the walls of the vessels. These are discussed in the section on etiology.

Liver.—The lesions found in the liver depend on the duration of the thrombosis. In the acute stage there is severe venous engorgement, resulting in central lobular necrosis of hepatic cells. Later cirrhotic change develops, and nodular regenerative hyperplasia is common. Old and recent lesions are frequently found side by side in the same liver, confirming the clinical suggestion that numerous acute attacks of thrombosis are common.

In 3 cases (Nishikawa and Hutchison and Simpson) there developed primary carcinoma of the liver. There seems no doubt that this was the true interpretation, and it would appear reasonable to suggest that the carcinoma supervened on regenerative hyperplasia, as occasionally occurs in portal cirrhosis. An enlarged caudate (spigelian) lobe is frequent, as was noted by Nishikawa. It is probable that the thrombotic process misses the usually separate hepatic vein supplying this lobe, enabling compensatory hypertrophy to occur more readily.

Other Lesions—Thrombosis of the portal veins is a rare and usually terminal event. In 2 cases there developed an infarction of the intestines. The only other intestinal lesion noted is a varying degree of congestion. Apart from the vascular lesions mentioned in the next section, the changes described in the spleen are those of severe venous engorgement.

Nishikawa presented extensive charts of the venous anastomoses; these, however, appear too well known for review here.

RELATED EXPERIMENTAL WORK

Simonds and Callaway and Jergesen reported on the changes occurring in the livers of dogs after mechanical constriction of the hepatic veins for ten to fifty minutes. They found swelling and granulation of the hepatic cells, resulting later in complete sinusoidal collapse. Hyaline thrombi were found in many central and sublobular veins, and a large number of mononuclear cells were present, with some proliferation of the sinusoidal endothelium. The picture was reported as resembling the focal necrosis of typhoid. The authors emphasized the presence of lymphatic dilatation, only once mentioned as occurring in a human being (Ohno).

ETIOLOGY

Age.—The youngest patient with thrombosis of the hepatic veins mentioned in the literature is Gee's 17 month old patient. Unruh's patient was 1 year old, but in this instance the condition was due to endothelioma of the vena cava. The oldest patient mentioned was 61 years. The average in 86 cases in which age was mentioned was 34 years. Hess gave the average as 28.5 years.

Sex.—Of 88 patients for whom the sex was recorded, there were 50 males and 38 females. This does not agree with previous statements, since Byrom remarked that the condition is twice as common in females and Rolleston that the sexes are equally affected.

Predisposing Diseases.—The syndrome of thrombosis of the hepatic veins may be due to a variety of disease processes; moreover, there can be no doubt that in any one case several factors are usually active. There may be a general disease, such as polycythemia, carrying a pronounced tendency to thrombosis, which in combination with a minor local lesion will cause thrombosis of the hepatic veins. Conversely, there may be a gross local lesion with a minimal general disease. Some of these factors, both general and local, will be considered.

A congenital vascular fault may be the local factor in thrombosis occurring in early life but is not likely to be present in the majority of patients in the older age groups. The theory that there is spread of the obliterative process from the ductus venosus to the hepatic veins, suggested by Moore and Rolleston, has no supporting evidence. The presence of a congenital venous anomaly, such as a valvular fold, is a possibility but would be extremely difficult of proof. The theory of Kretz that repeated trauma, such as occurs because of the coughing in pertussis, might lead to tearing of the venous walls and to subsequent thrombosis has nothing to commend it. The diagnosis of primary peri-

tonitis leading to periphlebitis, as postulated by Mann and Hall and Frerichs, is excluded in all but their cases by the absence of any peritoneal reaction except the mild one so common in long-standing ascites. Venous block by gumma was reported by Fagge, West and Wilks; however, gummas of the liver are now extremely rare, and in all recent cases syphilis can be ruled out by a negative reaction to the Wassermann test. Hart reported an instance of death resulting from treatment with arsphenamine in which miliary granulomas were found around the small hepatic veins and suggested that such lesions might give rise to thrombosis of the hepatic veins. It appears likely that these lesions were really those of a necrotizing arteritis due to hypersensitivity to the arsenical compound. Hart's concept, however, is interesting, and further remarks about general vascular disease as a cause will be made in this article.

Terminal thrombosis related to hepatic suppuration is recorded by Winternitz and Visconti and also occurred in a case in the Massachusetts General Hospital. While this condition is of pathologic interest, it is terminal and is of no clinical interest.

Thompson and Turnbull suggested that eddying of the streams of blood at the junction of the hepatic veins with the vena cava might explain the many cases in which the thrombosis occurred at the ostiums of the hepatic veins; marked obliquity of the entering veins is a possible added factor. It is generally accepted that at the site of alterations in caliber or at the confluence of blood streams deposition of cells and fibrin may occur on the walls of vessels. The authors remarked that such changes are extremely rare at the ostiums of the hepatic veins, but they reported a case in which there was a projecting ledge of thrombus at the venous junction, just where the main block so often occurs in the Chiari syndrome. There seems no doubt that this theory adequately accounts for the great frequency of thrombosis at the hepatic vein ostiums, but other factors must be present to a greater or lesser degree.

Also among general causes for the syndrome must be placed diseases in which there is a well recognized tendency toward thrombosis. There are in the literature 8 cases of polycythemia vera in which the syndrome occurred (Altschule and White, Baehr and Klemperer, Berk, Cole, McAlpin and Smith, Oppenheimer and Ulhorn). Relation of the onset of the illness to pregnancy has been noted four times (Chiari's case 1, Coronini and Oberson's case 8, Lange's case and Nagayo's case 3). I have recently observed a case of leukemia in which thrombosis of the veins of the right lobe of the liver had occurred.

A further probable cause is phlebitis of the hepatic veins, with cellular infiltration of the media, intimal thickening and superimposed thrombosis. Hess, Meyer, Ohno, Pacher and Satke brought forward

strong evidence of this. There seems no doubt that in certain cases it is one of the main local factors leading to thrombosis of the hepatic veins.

Coronini and Oberson expressed the most interesting view, that thrombosis of the hepatic veins can result from a general vascular disease. They found inflammatory changes in the intima of the hepatic veins of a serofibrillary character, often with well defined medionecrosis. The generalized nature of the disease is supported by the finding of similar lesions in the radicles of the portal veins and in the splenic vasculature, resulting in a "fibro-adenie" resembling that described in Banti's syndrome. More rarely the pancreas and the kidney may be affected, and the authors described tissue damage in the heart of the type seen in rheumatism. Stressing the type of the vascular lesions, they suggested a rheumatic basis for thrombosis of the hepatic veins, i. e., an allergic tissue reaction in the sense of Klinge and Rossle.

CLINICAL FEATURES

Abdominal Pain.—Usually pain is the initial symptom. It precedes hepatic enlargement and ascites and is one of the most constant features. It differs in severity, varying from mild discomfort and "indigestion" or a sense of pressure to a severe cramping pain. It is usually epigastric, with predominance under or over the right costal margin, and sometimes radiates to the back and the loins. Some reports mention the occurrence of attacks of pain for years before the final illness, but it appears likely that these represent minor episodes of thrombosis. Sudden stretching of its capsule by the engorged liver substance would appear to be the explanation of the pain.

Ascites.—Large quantities of transudate, occasionally hemorrhagic and rapidly recurring after paracentesis, are usually found. In 5 cases ascites was absent clinically, but in 3 of these it was found at autopsy or on laparotomy. In 1 case death occurred at five days, and there may not have been time for an ascitic collection to develop. It is to be assumed that the development of an adequate collateral circulation is the explanation, and it is of interest that in several cases in which there had been earlier gross ascites there was little fluid at autopsy.

Hepatic Enlargement.—Hepatic enlargement is usually striking, but difficulty in palpation is frequent owing to massive ascites. However, the organ is generally readily palpable after paracentesis. A rapid, tender enlargement is usual, extending as a rule to two or three finger-breadths below the costal margin. In cases in which the disease is of longer duration, the edge recedes, tenderness passes off and the organ becomes harder as cirrhotic changes develop. It is usually smooth and firm, but in a few cases irregular masses due to primary or secondary carcinoma of the liver have been palpable.

Splenic Enlargement.—Enlargement of the spleen is not nearly so frequently noted clinically as is hepatic enlargement. It is not usually gross, extending as a rule about a fingerbreadth below the costal margin. In only 1 atypical case was it of considerable degree.

Venous Collaterals.—The presence of venous collaterals is one of the most important signs. Usually the enlargement is over the upper part of the abdomen and the lower part of the thorax, especially near the xiphoid cartilage, where anastomosis between the superior epigastric, medial xiphoid and internal mammary veins takes place; only a few reports mention a caput medusae. The presence and size of these anastomotic veins are related to the duration of the thrombosis. The few reports mentioning this point suggest that a few weeks are necessary for the development of obvious dilatation. In the second case reported on here the dilatation appeared almost immediately after the thrombosis. In the early stages there may be only dusky engorgement of fine vessels, giving a cyanotic hue. Pleasants pointed out that if there was thrombosis in the vena cava the lower the thrombosis extended, the lower were the collaterals on the abdominal wall.

Edema of the Legs.—Edema of the legs was present to a greater or lesser degree in 43 cases. In many it was transient or limited to the feet. Considerable edema, especially if it extends to the thighs, should strongly suggest that the thrombosis has involved the vena cava. This statement, of course, implies exclusion of other general causes of edema.

Jaundice.—The absence of gross jaundice and the presence of the slight, latent or clinical form are the most important features. Reports vary in their statements on this point, some denying the presence of jaundice, others referring to subicterus. In the few cases in which detailed examination was made, mild icterus was demonstrated. The van den Bergh test has shown an increased indirect value. Six reports mention the occurrence of increased urobilin in the urine, or occasionally of bile. There is too little available information to enable definite figures to be given.

Other Evidence of Hepatic Damage.—Unfortunately, only 5 case reports refer to tests of hepatic function. Sohval mentioned low plasma cholesterol levels, with only a trace of ester fraction. Kahn and Spring noted a cholesterol level of 173.9 mg., and Goldstein a level of 166.3 mg. Satke reported negative reactions to galactose tests in 2 instances, with a positive reaction to the tetrachlor-phenolphthalein test in 1; in the latter instance scanty amounts of leucine and tyrosine were found in the urine.

Vomiting.—Vomiting is mentioned in about one quarter of the cases, usually being most severe at the time of an acute episode.

hematemesis is rare; in most cases it is clearly due to varicose esophageal veins. Melena or rectal bleeding is even rarer.

Diarrhea.—Only five references to diarrhea were found. In 2 cases it was diffuse and watery and may have been related to edema of the bowel wall.

Dyspnea.—Dyspnea is a frequent symptom in cases of massive ascites, being due to upward displacement of the diaphragm.

Pleural Effusion.—This is rare and usually terminal.

Neurologic Signs.—Several authors have mentioned the occurrence of a drowsy state drifting into the picture of cholemia in the terminal stages. Goldstein reported a case in which there were striatal signs. There was a masklike face, poverty of eye movements, monotonous speech, salivation, tremor of the extremities, an oculomotor palsy and left trigeminal hyperalgesia. Striatal lesions resembling those seen in postencephalitic parkinsonism were found at autopsy. This case is a further example of the interesting relation between striatal disease and hepatic damage.

Renal Damage.—Evidence of this is exceptional. Altschule and White reported a case of terminal uremia; however, even in cases of caval thrombosis there is no renal abnormality, as the thrombus is almost invariably in the upper part of the vessel.

Clinical Features of Minor Thrombosis.—The features just described apply to the classic Chiari syndrome with well defined venous block. In other cases the thrombosis is much more limited but may be repeated over years until the full clinical picture emerges. It would be well to bear in mind the diagnosis of thrombosis of the hepatic veins in the presence of obscure pain in the upper abdominal area, especially if there are even minor signs of hepatic damage and if there are points in the history which make a diagnosis of infective hepatitis unlikely. If such an incident should occur in the course of some disease in which thrombosis is common, then the diagnosis would be even more worthy of consideration.

DIFFERENTIAL DIAGNOSIS

The first correct diagnosis was made by Willcocks in 1896. Since then the syndrome has been diagnosed during life in 10 cases, including the 2 cases presented here. The great majority of cases present such a typical picture that there are not many other diseases closely resembling it. There are a few atypical cases in which diagnosis is difficult, such as the 5 in which there was no ascites and Satke's case 4 which appeared to be an instance of isolated splenomegaly. In cases in which the thrombosis occurs as a terminal event diagnosis is impossible.

Thrombosis of the portal veins presents similar features, including sudden onset with pain, ascites and the later development of anastomotic veins. The essential point of difference is the absence of hepatic enlargement and even the minor manifestations of jaundice in uncomplicated cases of portal vein thrombosis. In portal cirrhosis the clinical picture lacks the drama of thrombosis of the hepatic veins. Jaundice if present either will be or will become more pronounced than it is in the Chiari syndrome. The history of a case of cirrhosis is frequently suggestive of the diagnosis, and the age incidence is rather different. Confusion with carcinomatous or tuberculous peritonitis and with adhesive pericarditis is not likely.

PROGNOSIS

The duration is variable, but, as Thompson and Turnbull stated, there are two main groups. In the majority of cases the disease is of short duration, in some lasting only a few days. In the smaller group the disease may last from ten to twenty-eight years. Even in this type, however, there is often a story of a recent sudden episode. Chiari's second case is a good example of this, and examples will also be found in Rolleston's discussion in the paper by Hoover and in the paper by Hutchison and Simpson.

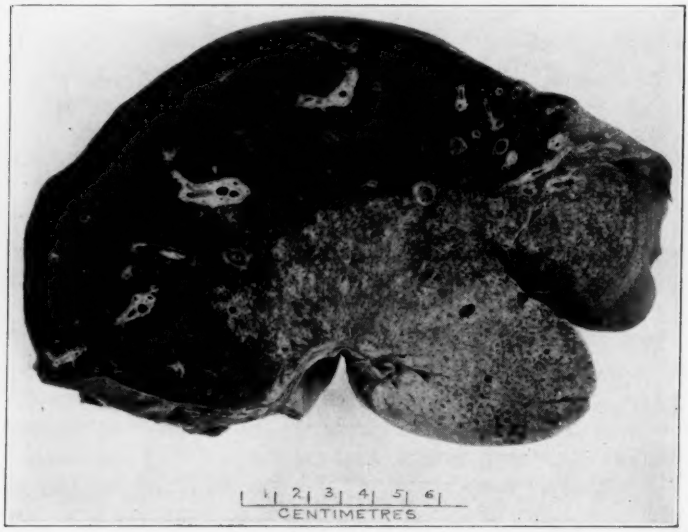
TREATMENT

The treatment of this disease unfortunately does not offer much scope for discussion. It must be on the same lines as the treatment for portal cirrhosis. Byrom's suggestion that paracentesis accelerated death does not appear correct. One gathers that the few patients who did die after tapping were extremely ill before the operation. One point of great importance is that, although this is an extremely fatal disease, patients may live for many years before succumbing, perhaps to a fresh thrombosis. There is no doubt that the fatal termination can be greatly accelerated by operative intervention. Of 9 patients who were operated on, 8 died, the majority within two to three days and 2 within twelve hours.

REPORT OF CASES

CASE 1.—*Clinical History.*—The patient was a miner 31 years of age. He had been in good health all his life, apart from occasional bouts of abdominal pain and diarrhea, until three weeks before his admission to the hospital. He went to work one morning feeling well, but during the day he began to have such severe pain in the abdomen that he was obliged to return home, and by the evening he felt so ill that he had to retire to bed. On attempting to dress the following morning, he found his abdomen so swollen that he was unable to put on his trousers. During the period prior to his admission, the swelling progressed more slowly. After the first few days, pain was not so prominent. There was no vomiting or diarrhea, and his appetite was good.

On his admission to the hospital there was gross ascites, respiration being embarrassed by upward pressure on the diaphragm. On the upper abdominal wall a few enlarged veins could be seen. After paracentesis, an extremely hard, nontender liver could be felt, and no splenic enlargement was noted. There was no edema of the legs. Tapping was carried out three times, a total of 31 liters of pale fluid with a protein content of 1.0 per cent being removed. The liver edge receded during this period, and increasing hardness was noted. There was only slight jaundice immediately before death. No abnormal physical signs were found in the cardiovascular system, lungs or nervous system. Examination of the stools persistently revealed occult blood. The Wassermann reaction was negative. During the last few days of his illness, the patient relapsed into a comatose state, and the mode of death was that so commonly seen in severe necrosis of the liver.



Photograph of a section through the liver in case 1. To the left is the greatly engorged, recently involved right lobe. In the hepatic veins can be seen thrombi of varying ages. To the right is the mass of accessory hepatic tissue, and the large lobules are clearly shown. Above and to the right is a portion of the left lobe grossly scarred from long-standing infarction.

Several diagnoses were considered. Infective hepatitis was excluded by the absence of pronounced jaundice coupled with the presence of recurrent gross ascites. A diagnosis of cirrhosis did not seem tenable for a previously healthy man with a remarkably rapid onset of disease accompanied with pain. The hepatic enlargement made an uncomplicated portal thrombosis most unlikely. The history alone appeared to rule out the diagnosis of a neoplastic process, as did the type of peritoneal fluid. It was felt that the history and clinical findings were so strongly suggestive of thrombosis of the hepatic veins as to warrant a diagnosis of the Budd-Chiari syndrome.

Abstract of Autopsy Report.—The body was that of a well developed but poorly nourished subject. The peritoneal cavity contained about 0.5 liter of clear yellow

fluid. The visceral and parietal peritoneum and the intestines were a dusky red from considerable dilatation of large veins, closely set venules and capillaries. The parietal pleura showed the same engorgement, but the pleural sacs contained no fluid. In the subcutaneous tissues of the lower part of the chest there were many dilated venules. The pectoral muscles showed similar changes, and in addition there were numerous dilated veins. The internal mammary veins were slightly dilated; seven trunks were present. The azygos vein was dilated, having a diameter of 1.5 cm. There was no evident caput medusae, but there were well marked attempts at a collateral circulation in the usual sites. In the pericardium and anterior mediastinum there were many dilated veins and capillaries. The superior vena cava had a circumference of 6.0 cm. just before entering the auricle; the innominate veins were not obviously dilated. The right side of the heart was much dilated; however, beyond a little myocardial scarring there was nothing remarkable. The inferior vena cava showed a vestigial valve 5.0 cm. long and up to 1.5 cm. broad; at 6.0 cm. below the diaphragm the vessel was 8.0 cm. in circumference. There were no thrombi present. The ostiums of the hepatic veins seemed smaller than normal, and one of the superior group had protruding from it a piece of antemortem clot 0.6 cm. long. The liver appeared reduced in size but weighed 1,650 Gm. The right lobe had a finely granular and wrinkled exterior and was dark bluish. On section its lateral half showed occlusion of practically all the hepatic veins by recent, or at least recently organized, thrombi. In the medial portion practically all the hepatic veins were filled by pale, firm, organized thrombi; in some, recanalization was apparent to the naked eye. Recent thrombi were infrequent.

The liver itself was a dark plum color and was firm. Lobular markings were usually not made out; when they were, they indicated small lobules. The appearance was that of so-called red infarction. In the lateral portion were a few scattered yellowish foci of "normal" liver, 0.2 cm. or so in diameter. Springing from the under surface of the right lobe, some 5.0 cm. from its right margin, was an irregular tubular mass of accessory hepatic tissue. It had a rounded termination and constituted one third to one half of the liver mass, measuring 12 by 10 by 6 cm. Its line of demarcation from the rest of the right lobe was irregular but sharply defined. Unlike the other lobes, it was covered by a smooth thin capsule, had a yellowish color and was extremely soft.

The left lobe was reduced in size, being only 2.5 cm. long and 5.0 cm. broad. Its external appearance resembled that of the right lobe, but one third of it was occupied by a pale, depressed, scarred, triangular area. On section most of it resembled the medial portion of the right lobe, but the triangular scarred area contained only a few recognizable vessels and no hepatic cells.

Microscopically the hepatic veins, particularly the large trunks, showed thrombi of varying ages. Some were recent, although even these were organized. Others were old and fibrosed, and in these channels of recanalization often showed recent thrombi. Inflammatory changes were not evident. Hepatic tissue in the distribution of the thrombosed veins had disappeared, apart from a thin layer of cells around the portal tracts. The tracts themselves showed an increase of fibrous tissue, and early bile duct proliferation was present near them. In the accessory lobe the lobules were enormous and large vessels and portal tracts were absent, confirming the microscopic appearance of regenerated liver. The spleen was much enlarged, weighing 640 Gm., and the sinusoids were distended by blood. There was an old infarct measuring 5 by 3 cm., with microscopically a number of smaller deep infarcts such as might arise as a result of venous lesions. The kidneys were enlarged (400 Gm.) and showed intense congestion, and there was scanty exudate in some

capsular spaces. The jejunum was edematous and intensely congested, as were the ileum and large intestine.

CASE 2.—*Clinical History.*—A previously healthy girl of 2 years of age took ill suddenly a month before her admission to the hospital, with cyanosis, panting respirations and vomiting. From this she recovered in three days and was well again until six days before her second admission, when abdominal pain developed, lasting a few hours and followed by rapid swelling of the abdomen and, on the next day, of the legs. There was no diarrhea or vomiting. She was found to be extremely pale, with gross edema of the lower extremities and of the abdomen up to the costal margin. There was decided tenderness over the liver area, and she was evidently in great pain, screaming during the examination. A large ascitic collection made visceral palpation difficult, but a tender, smooth liver was palpable three fingerbreadths below the costal margin; the spleen could not be felt. Distended veins coursed upward over the right costal margin. The abdominal circumference at the umbilicus was 22 inches (56 cm.). There were no other abnormal clinical findings. During the first few days following her admission, the patient's condition improved, and the liver diminished in size and tenderness. On the basis of these symptoms, a diagnosis of thrombosis of the inferior vena cava and the hepatic veins was made. Later the abdominal collateral veins became more and more obvious, extending from the lower third of the abdomen to above the costal margin, and lumbar veins also became noticeable. By two paracenteses 12 pints (5.6 liters) of pale yellow transudate were removed. After a fluctuating illness the patient eventually died, fourteen weeks after her admission to the hospital. There had never been any clinical evidence of jaundice, but, unfortunately, no biochemical evidence was sought. The serum protein content ranged from 4.2 Gm. per hundred cubic centimeters (albumin 3.12 Gm., globulin 1.08 Gm.) to 5.23 Gm. (albumin 3.32 Gm., globulin 1.91 Gm.). The lower figure was the initial one, suggesting that hepatic damage was the cause and not loss of protein into the ascitic fluid.

Abstract of Autopsy Report.—The outward appearances were similar to those described during life, namely, massive ascites with large anastomotic veins on the abdomen. The peritoneum was normal, apart from some adhesions between the liver and the diaphragm; 6 liters of ascitic fluid was present. The liver weighed 855 Gm. (normal, 390 Gm.), fixed in solution of formaldehyde. There were many dilated veins between it and the diaphragm. Its surface appeared nodular, and on section it showed necrosis of large portions, with localized areas of regeneration confined largely to the center of the right lobe. Several occluded hepatic veins could be seen, and the picture suggested hepatic necrosis secondary to venous obstruction. Histologically the liver showed marked atrophy of the greater part of the lobules, many showing only a rim of surviving cells. In a few areas there were nodules of regenerating liver. There was little fibrosis of the portal tracts. In association with a few recently thrombosed hepatic veins there was great congestion of the sinuses. The inferior vena cava was examined histologically at levels from the diaphragm to the renal veins. In the intrahepatic portion there was evidence of previous thrombosis, with organization and recanalization. The main hepatic veins entering the vena cava showed complete blockage by organized thrombus, with little recanalization. The greater portion of the vena cava at this level was patent, and the wall showed no abnormality except in relation to the organization, in which areas the muscle was thinned and in places almost completely absent; the elastica in these areas was also scanty. The part of the vena cava below the liver was narrow, with a diameter of 5.0 cm. Just above the level of the renal veins

the lumen of the vena cava was occupied by crisscross bands of fibrous tissue, which was due to organization of the thrombus: in the meshes were several recent thrombi. The renal veins were themselves free, but the right vein showed evidence of an old mural thrombus, and there was an old infarct in the kidney. At one point there was a slight proliferation of the intima of the renal artery. The spleen weighed 83 Gm. (normal, 37 Gm.); there was moderate pulp congestion with prominent germ centers. The esophageal veins were rather more prominent than usual, but they showed no varicosities. A small myocardial artery showed pronounced intimal proliferation, without reduplication of the elastica.

COMMENT

Case 1 clearly shows the result of repeated thromboses over a long period. The triangular area in the left lobe of the liver was evidently of long duration. The rest of the lobe and the medial portion of the right lobe had been more recently involved, and the lateral portion of the right lobe more recently still. It is interesting in this respect to recall the attacks of abdominal pain. The thrombosis had evidently occurred in the hepatic veins near the ostiums, but unfortunately all the thrombi were so old that no conclusions could be reached as to their pathogenesis. The splenic infarcts strongly suggested that there had been involvement of the veins in the spleen as well as of those in the liver; there was no evidence of vascular lesions in other organs. The possible relation of the vestigial valves to the thrombosis is of interest.

In the second case the thrombosis probably commenced about the ostiums of the hepatic veins and spread to the cava and to the hepatic veins proper. Here again the age of the thrombi obscured their pathogenesis, but support for the theory of a general vascular disease was given by the renal infarct, the nature of which suggested a venous thrombosis as the cause, and by the vascular lesion in the myocardium.

SUMMARY

Two cases of the Chiari syndrome have been reported and 95 reviewed. It is concluded that the syndrome may result from a number of disease processes, and an attempt is made to clarify these and also to define the clinical picture. It is also suggested that minor degrees of thrombosis of the hepatic veins occur and that the diagnosis should be borne in mind in cases of obscure pain in the upper abdominal area, especially when there is any evidence of hepatic damage.

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NITROGEN AND FLUID BALANCE IN TREATMENT OF ACUTE UREMIA BY PERITONEAL LAVAGE

Analysis of Peritoneal Washings for Protein, Nonprotein Nitrogen and Phosphorus

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A NUMBER of experiments have been conducted to test the possibilities of using the peritoneal surfaces in vividialysis.[1] The basis for this work is the well established fact that water, crystalloids and some colloids including plasma proteins are readily absorbed by the

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lining membranes of the serous cavities.[2] It has been demonstrated further that intact erythrocytes labeled with radioactive iron [3] rapidly leave the peritoneal space of the dog by way of the lymphatic vessels of the diaphragm and subsequently appear in the peripheral blood. Fortunately, in the absence of inflammation or tumor the passage of formed elements of the blood in the reverse direction is minimal and the concentration of protein in peritoneal transudates is low.[4] Equilibrium between crystalloids of the interstitial fluids is established rapidly when various isotonic or mildly hypertonic and hypotonic fluids are injected into the abdomen.[5] For this reason, lavage of the peritoneum has been performed in man on a few occasions in an attempt to relieve the intoxication of uremia.[6] Although the number of reported survivals is small (two), with a practical procedure for peritoneal irrigation, such as that described by Fine and others,[6b] and a more careful selection of cases one may anticipate better results. We desire to report treatment of a patient who died but on whom it was possible to obtain considerable data on the nitrogen and fluid balances during a period of continuous peritoneal irrigation for twenty-one days after the onset of almost complete anuria.

REPORT OF A CASE

A single white woman of 24 years of age became ill on Dec. 16, 1945, with nasopharyngitis caused by beta hemolytic streptococci. Four weeks later swelling

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of the hands was noted, the blood pressure was elevated and protein was discovered in the urine. Her general condition failed to show improvement, and she was hospitalized about ten weeks after the onset of the original illness.

Examination revealed pallor, generalized edema and elevation of the blood pressure to 165 systolic and 110 diastolic. Retinal edema, areas of arterial spasm and scattered areas of cotton wool exudate were present in the fundi. The specific gravity of the urine was 1.020, the test for protein gave a reaction of 4 plus and the sediment contained many red blood cells and hyaline casts. There was slight anemia, with a hemoglobin content of 13 Gm. per hundred cubic centimeters of whole blood and 3,800,000 red blood cells and 10,300 white blood cells per cubic millimeter. The differential count showed 88 per cent neutrophils, 8 per cent lymphocytes and 4 per cent monocytes. Study of the blood chemistry revealed a nonprotein nitrogen content of 48 mg. per hundred cubic centimeters and a serum protein level of 4.2 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.0. The electrophoretic patterns of the blood plasma and urinary proteins were determined later and were as follows:

	Plasma Protein, %	Urine Protein, %
Albumin*	1.02	0.69
Globulin		
α_1	0.57	0.39
α_2	1.30	?
β	1.68	0.15
ϕ	0.64	0.00
γ	0.68	0.17
Total	5.89	1.40

* It will be noted that the albumin fraction was much lower when the plasma proteins were fractionated by electrophoresis. In our experience this discrepancy between the chemical and electrophoretic methods of separation of albumin from globulin occurs frequently in abnormal serums. Howe's procedure was used in the chemical separation in this case.

During the course of twenty-four hours, 1.1 Gm. of gamma globulin was excreted in the urine—about 5 per cent of the total circulating gamma globulin.

Because of maxillary sinusitis, penicillin was administered intramuscularly for fourteen days to a total dose of 2,225,000 units. Toward the end of the period it was found that the in vitro resistance of hemolytic streptococci originally cultured from the throat was high to both sulfadiazine and penicillin (60 mg. per hundred cubic centimeters for sulfadiazine and 10 units per hundred cubic centimeters for penicillin).

An attempt was made to control edema by restricting the intake of fluid and salt, but this was not successful on the general ward, and the patient was transferred to the metabolic unit on March 23. The hemoglobin content had now decreased to 10.5 Gm. per hundred cubic centimeters. Total plasma protein was 5.1 Gm. per hundred cubic centimeters.

Attempts to provide an adequate caloric and protein intake were frustrated by nausea and vomiting, and it was soon apparent that the patient's general condition was deteriorating. On April 4 it was decided to administer ammonium chloride in the hope of producing diuresis. Eight grams were given in divided doses on April 5 and 2 Gm. on April 6. The volumes of urine for April 5, 6 and 7 were 1,200, 1,400 and 1,200 cc. respectively. Administration of ammonium chloride was discontinued on April 6. Chemical examination of the blood on this date showed the nonprotein nitrogen to be 48 mg. per hundred cubic centimeters, total plasma protein 5.4 Gm. per hundred cubic centimeters, chlorides 104 milliequivalents, and cholesterol 467 mg. per hundred cubic centimeters. The last spontaneous voiding of urine was at 11 p. m. on April 7. On April 8 she was given a transfusion of 575 cc. of con-

centrated plasma containing 69.8 Gm. of protein. The temperature rose about 1 degree (C.) during the infusion and thereafter remained at about 38 C. (100.4 F.). The nonprotein nitrogen had now risen to 127 mg., and the carbon dioxide was 20 volumes per cent.

From this point on the greatest volume of urine obtained in a single twenty-four hour period was 132 cc. Fluids given orally were promptly vomited. Between April 8 and 10, 3,500 cc. of fluid was given parenterally, of which 500 cc. was one-sixth molar sodium *r*-lactate and 3,000 cc. was 5 per cent dextrose. Chemical examination of the blood April 10 gave these values: nonprotein nitrogen 135 mg. and creatinine 14.4 mg. per hundred cubic centimeters, carbon dioxide 29 volumes per cent, chlorides 95 milliequivalents and total plasma protein 5.8 Gm., calcium 8.7 mg. and inorganic phosphorus 14.9 mg. per hundred cubic centimeters.

We were uncertain as to the cause of the rather abrupt cessation of urine formation and wondered whether it denoted an acute exacerbation of subacute glomerulonephritis. Hoping that renal function might be reestablished in a few days if the patient could be carried through this critical period, we decided to

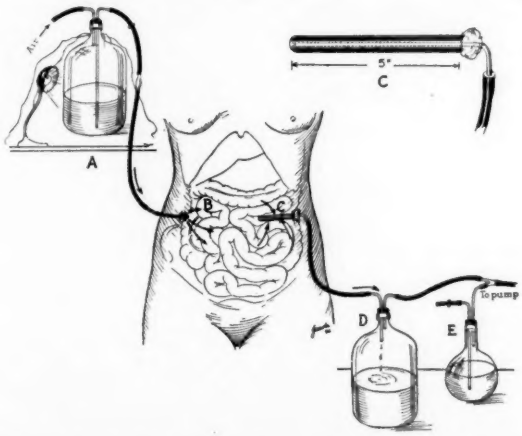

Fig. 1.—Scheme for peritoneal irrigation. *A* is reservoir of Tyrode's solution kept warm by electric light bulb. *B* is pesar catheter through which fluid was introduced by continuous drip from reservoir *A*. *C* is fenestrated brass tube entering peritoneum and serving as the "sump drain." A glass tube about half the diameter of the "sump" was passed nearly to the bottom of the brass tube and connected by rubber tubing to the collection bottle *D*. Suction was applied by a small electric pump (not shown) and the vacuum adjusted by permitting air to flow through the tube immersed in water of flask *E*.

irrigate the peritoneal cavity, following the procedure outlined by Frank, Seligman and Fine.[7] Accordingly, the patient was removed to the operating room, and Dr. Earle Mahoney inserted a Pesar catheter into the right flank and sutured a "sump drain"[8] to the skin, with its free end extending into the peritoneal cavity on the left

7. Frank, H. A.; Seligman, A. M., and Fine, J.: Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation, J. A. M. A. **130**:703 (March 16) 1946.

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(fig. 1). It was thus possible to introduce Tyrode's solution by continuous drip into the right side of the abdomen and withdraw it by gentle suction from the left side. Wangensteen suction was likewise applied through a tube introduced into the stomach. This prevented vomiting and helped to combat distention.

The composition of the perfusing fluid was kept constant except for the dextrose, which was altered depending on the degree of hydration or dehydration of the patient.[1a] When the concentration of dextrose was low (0.1 per cent) there was a tendency for fluid to be retained, while with concentrations of 1 to 2 per cent the amount of solution withdrawn usually exceeded the quantity entering the abdomen. For the first two weeks of the procedure it was possible to keep a fairly good record of the daily exchanges of fluid, but after this leakage occurred about the inlet catheter and unknown amounts of solution were lost on the dressings and into the bed.

Clinical Course (fig. 2).—The low grade fever, which had its inception two days before lavage was started, continued until death. Tachycardia, recurring pericardial

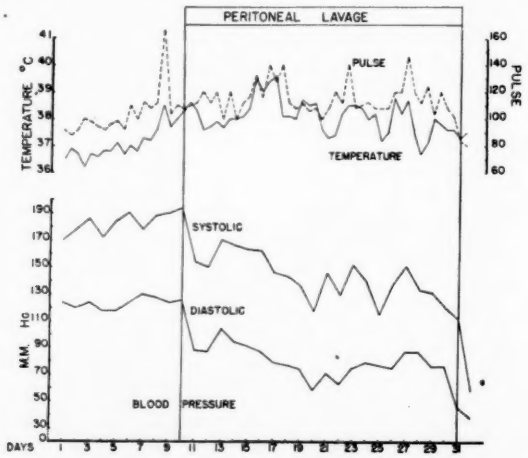

Fig. 2.—Chart of temperature, pulse and blood pressure.

friction rub, leukocytosis as high as 33,000 per cubic millimeter and intermittent delirium were also noted. The blood pressure was 194 systolic and 124 diastolic at the onset of anuria. Seven days after abdominal perfusion was begun, it had fallen to 140 systolic and 80 diastolic. It was at this time that the patient appeared distinctly improved. The duration of improvement coincided well with the fall in the levels of nonprotein nitrogen and phosphorus (fig. 3). Hypertension did not recur with increasing azotemia.

Until most of the superficial veins became thrombosed, much of the intake was intravenous. The patient was allowed to drink water freely, but a considerable part of it was returned through the Wangensteen suction. The amount of plasma protein given by vein, exclusive of plasma of whole blood, was 623 Gm. (April 11 to 17), and administration was then discontinued. Whole blood transfused between April 11 and 23 amounted to 2,000 cc. Additional fluid in the form of one-sixth molar sodium *r*-lactate totaled 6,300 cc. given during the first twelve days. It

appears to be of some interest that the transudation of protein into the abdomen was greatest at the time plasma protein was being administered in large quantities. The amount of protein transfused was 623 Gm. and the amount removed 506 Gm. Vitamins were given parenterally daily, as follows: 200 mg. of ascorbic acid and 10 cc. of a soluble vitamin B preparation containing thiamine chloride, 10 mg. of riboflavin, 5 mg. of pyridoxine hydrochloride, 50 mg. of calcium pantothenate and 250 mg. of nicotinamide. Penicillin in the amount of 15,000 units was given intramuscularly every three hours, and about 100,000 units in isotonic solution of sodium chloride was used daily to apply to dressing covering the abdominal wounds. Additional penicillin was given in the irrigation fluid. Phenobarbital sodium, codeine sulfate and dihydromorphinone hydrochloride were employed as required for sedation and pain. A 10 per cent solution of "aminoids" (an oral protein concentrate in liquid form) was given by stomach tube at fairly regular intervals after the seventh day. Most of it seemed to remain in the stomach and had to be withdrawn

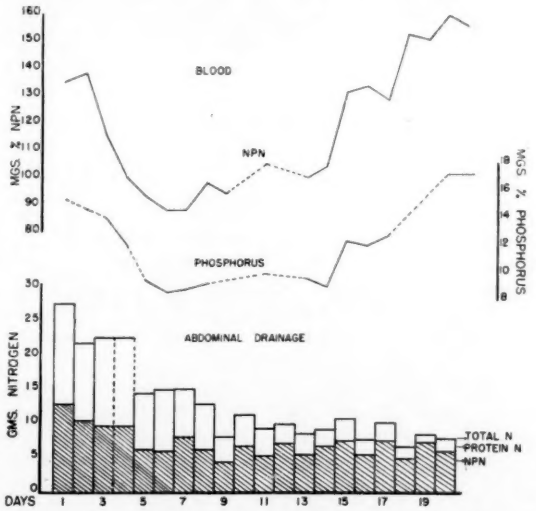

Fig. 3.—The columns represent the total amount of nitrogen removed each twenty-four hours by peritoneal irrigation. The clear portions correspond to the fraction of the total nitrogen derived from protein; the cross hatched part represents nonprotein nitrogen. Above are shown the levels of nonprotein nitrogen in whole blood and the inorganic phosphorus levels in the serum.

within the hour. The patient was relatively intolerant also of a high caloric liquid formula which was tried after infusions were discontinued.

Edema became gradually worse at first, probably because the oral intake was greater than that recorded in the table of water balance (table 1). After the tenth day the weight began to decline, and during the last few days of life the edema had largely disappeared. It was obvious that the patient had drawn heavily on her reserves of fat, but she never appeared emaciated. During the last four or five days of life she became gradually weaker. Frank pulmonary edema did not develop, but scattered rales were heard throughout both lungs. Death occurred rather suddenly on the twenty-first day after peritoneal irrigation had been initiated. The exact

TABLE 1.—*Fluid Balance**

Date, 1946	Hours	Fluid Intake				Fluid Output				Body Weight, Kg.
		Oral, Cc.	Intravenous, Cc.	Peritoneal, Cc.	Total Approximate, Cc.	Urine	Peritoneal Drainage, Cc.	Wangensteen Drainage, Cc.	Skin and Lungs, Cc.	Total Approximate, Cc.	
4/ 6	..	.....	.....	.....	.....	...	.....	.....	.....	.....	69.86
4/10 to 4/11	24	970+	1,500	13,120	15,590	...	13,060	1,100	1,000	15,160	.....
4/11 to 4/12	24	2,100+	2,000	12,580	16,680	132	13,140	2,300	1,000	16,572	.....
4/12 to 4/15	62½	3,560+	4,850	22,880	31,290	79	28,060	2,890	2,600	33,629	.....
4/15 to 4/16	24	2,525+	525	5,600	8,650	58	7,760	2,970	1,000	11,787	.....
4/16 to 4/17	24	1,350+	1,700	5,880	8,930	60	7,950	1,685	1,000	10,695	.....
4/17 to 4/18	24	1,515+	2,520	12,200	16,235	26	13,560	2,380	1,000	16,966	.....
4/18 to 4/19	24	1,595+	2,820	7,660	12,075	32	8,570	2,350	1,000	11,952	.....
4/19 to 4/20	24	1,350+	2,500	12,250	20,350	28	4,570	2,700	1,000	19,277	.....
4/20 to 4/21	24	2,450+	1,800	15,570	23,720	19	7,580	2,380	1,000	20,791	73.5
4/21 to 4/22	24	1,350+	2,500	15,570	23,720	31	5,830	1,670	1,000	20,791	.....
4/22 to 4/23	24	1,550+	2,750	13,390	17,500	40	9,370	1,850	1,000	21,802	.....
4/23 to 4/24	24	2,120+	.....	13,390	17,500	58	5,880	3,960	1,000	21,802	.....
4/24 to 4/25	24	1,990+	.....	.....	.....	44	6,520	3,340	1,000	12,428	.....
4/25 to 4/26	24	1,950	.....	Leak	.....	48	9,480	1,900	1,000	12,428	.....
4/26 to 4/27	24	1,950	.....	Leak	.....	53	5,580	1,520	1,000	8,153	.....
4/27 to 4/28	24	2,580	.....	Leak	.....	39	8,560	3,200	1,000	12,799	.....
4/28 to 4/29	24	2,500	.....	Leak	.....	32	4,340	5,400	1,000	10,772	.....
4/29 to 4/30	24	1,065	.....	Leak	.....	14	7,770	3,490	1,000	12,274	58.9
4/30 to 5/ 1	24	2,490	2,100	Leak	.....	9	4,780	4,520	1,000	10,309	.....

* The fluid balance as given in this table is approximate. The oral intake is known to have been somewhat above the recorded value because of inaccurate measurement of drinking water. Leaking about the intake catheter occurred to some extent on April 24, and fluid thereafter escaped in unknown amounts before entering the peritoneal cavity. The values for output are reasonably correct except for losses from the skin and lungs, which have arbitrarily been assumed to be 1 liter a day.

reason for death is not known. We suspect that it was due to exhaustion and shock. Autopsy was limited to exploration of the abdominal cavity.

Observations at Autopsy (reported by Dr. Roger Terry).—The peritoneal cavity contained about 100 cc. of yellow turbid fluid, and the surface everywhere had a dull gray appearance. A fine granular layer of fibrin covered the loops of bowel. There was no evidence of a plastic exudate anywhere. The inner end of the mushroom catheter impinged on the right lobe of the liver. The "sump tube" rested in a small depression in the left psoas muscle. The omentum and several appendices epiploicae of the descending colon surrounded the inner aspect of the brass tube. Some of the fat tabs protruded through the perforations in the tube.

Stomach: There were numerous petechial hemorrhages in the mucosa in the region of the fundus. Two shallow ulcers were seen in this area.

Small Intestine: The entire wall of the small intestine appeared edematous.

Mesenteric Lymph Nodes: These were fairly large and yellowish.

Liver: Considerable fat was present in a periportal distribution in the liver. Kupffer cells in the central areas were loaded with fine yellow pigment granules.

Adrenal Glands: The left adrenal gland was of normal size and shape, and it was fairly firm. The cortex revealed a moderately thick yellowish outer zone, a thin, soft, brown inner zone and an inconspicuous gray medulla.

Kidneys: The right kidney weighed 180 Gm. and the left 215 Gm. There was a finely granular, reddish gray surface. Numerous dark red petechiae were clearly visible beneath the surface of the right kidney.

Microscopic Sections: Examination showed that all the glomeruli were altered. A few showed relatively little change except that the capillaries were bloodless or contained tiny pink thrombi, and there was some proliferation of the hyperchromatic epithelium. At the other extreme the glomeruli were almost completely replaced by fibrous tissue, with obliteration of the capillary tuft and proliferation of the basilar membrane. The tubules were generally dilated and filled by casts. The tubular epithelium was compressed and pale. Several small arteries contained organized thrombi. There was considerable proliferation of the intima of some of the large arteries.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: subacute glomerulonephritis; acute generalized fibrinous peritonitis; ulcerations and erosions of the gastric mucosa; fatty liver; edema and congestion of the gastrointestinal tract; edema of the retroperitoneal connective tissue and the mucosa of the urinary bladder, and mild dependent edema.

PREPARATION OF SOLUTIONS AND ANALYTIC METHODS

Tyrode's mammalian solution was prepared every twenty-four or forty-eight hours in quantities of 18 to 20 liters. The formula and additions are given in the accompanying tabulation. All the salts except bicarbonate were dissolved in somewhat less than the required volume of sterile distilled water. The sodium bicarbonate was dissolved separately and added slowly with stirring. No precipitation occurred so long as the solution remained cool. The salt mixture was now distributed in 4 liter Erlenmeyer flasks and autoclaved. A precipitate, probably magnesium and calcium carbonate, formed but was readily brought into solution again after the flasks had cooled by passing filtered carbon dioxide through each for a few minutes, using a sterile tube and other-

wise observing aseptic precautions. The autoclaved solution of electrolytes was transferred to a calibrated 20 liter pyrex bottle, and sufficient freshly prepared sterile dextrose solution was added to provide the desired concentration of sugar. Any deficiency in volume was made up by the addition of sterile distilled water, and the contents were mixed by gentle shaking. Penicillin sodium, sulfadiazine sodium and heparin were introduced just prior to the connection of the bottle with the irrigation system. The modified Tyrode's solution as used for peritoneal irrigation included the following:

NaCl	0.9%
KCl	0.02%
$CaCl_2$	0.02%
$MgCl_2$	0.01%
NaH_2PO_4	0.005%
$NaHCO_3$	0.05%
Dextrose	0.1 to 2.5%
Additions to each 18 liters	
Sulfadiazine sodium	2.5 Gm.
Heparin	100 mg.
Penicillin sodium	600,000 units

The following analytic procedures were used: the serum chloride content was determined by the open Carius method,[9] the carbon dioxide by the method of Van Slyke and Neill, the total protein by the micro-Kjeldahl method and the specific gravity by the copper sulfate method of Phillips and others.[10] The total nitrogen level of the drainage fluid was estimated by the micro-Kjeldahl method, the urea plus ammonia in the drainage fluid (probably almost entirely urea) by the method of Van Slyke and Kugel [11] and the total nonprotein nitrogen of the drainage fluid by the micro-Kjeldahl method after precipitation of the protein with trichloracetic acid. The protein nitrogen level of the drainage fluid was estimated as the difference between total nitrogen and nonprotein nitrogen. The nonprotein nitrogen content of the blood was determined by the method of Folin and Wu [9] and the phosphorus content of the serum and drainage fluid by the method of Fiske and Subbarow.[12]

DATA OBTAINED

Nitrogen, Phosphorus and Protein Contents of the Drainage Fluid.—In figure 3 we have indicated the quantity of nitrogen obtained by

9. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

10. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: The Copper Sulfate Method for Measuring Specific Gravity of Whole Blood and Plasma, Bumed News Letter **1**:1 (June 25) 1943.

11. Van Slyke, D. D., and Kugel, V. H.: Improvements in Manometric Micro-Kjeldahl and Blood Urea Methods, J. Biol. Chem. **102**:489, 1933.

12. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

analysis of the fluid drained from the abdomen by suction as well as the behavior of the whole blood nonprotein nitrogen and serum inorganic phosphorus. During the first seven or eight days, about half of the total nitrogen in the fluid obtained by abdominal drainage was from protein and about 80 per cent of the nonprotein nitrogen was urea plus ammonia. We believe that the protein was mainly plasma protein which diffused into the peritoneal cavity. The drainage fluid was clear or slightly opalescent, and except on two occasions, to be mentioned later, it was sterile on culture. Appreciable reductions in the level of blood nonprotein nitrogen and serum inorganic phosphorus were obtained. The lowest point occurred about the sixth day, and the reductions were maintained until about the fifteenth day, when the condition of the patient became worse. From the eighth day on, less protein was removed; the concentration of nonprotein nitrogen, however, remained about the same in the drainage fluid. The decrease in diffusion of protein into the

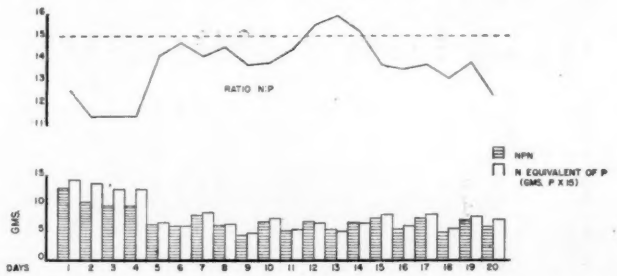

Fig. 4.—Nonprotein nitrogen and inorganic phosphorus levels of the peritoneal washings. Scale marked "Gms." refers to grams of nonprotein nitrogen in each day's collected peritoneal washings. The hatched columns represent nonprotein nitrogen of the drainage fluid, the clear columns inorganic phosphorus. The phosphorus has been plotted to a scale in which 1 Gm. of phosphorus equals 15 Gm. of nitrogen. The absolute ratio N : P is plotted as a line graph above.

abdominal cavity was not associated with any obvious lowering in the concentration of plasma protein (fig. 5), although it did coincide roughly with discontinuance of transfusions of plasma.

The amount of phosphorus removed was considerably greater than that entering with the perfusion fluid (fig. 4 and table 2). When corrections were made for the small quantity of phosphorus contained in the Tyrode solution, the ratio of nonprotein nitrogen to phosphorus was about what would be expected if protoplasm were being catabolized.[13] Although no analyses were made, it seems improbable that calcium was

13. Reifenstein, E. C., Jr.; Albright, F., and Wells, S. L.: The Accumulation, Interpretation and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus, and Nitrogen, J. Clin. Endocrinol. 5:367, 1945. Reid, Penfold and Jones.[6c]

TABLE 2.—*Exchange of Nitrogen and Chloride Through Gastric Intubation*

Date	"Aminoid" 10%, Cc.	"Aminoid" Nitrogen, Gm.	"Aminoid" Chloride, Gm.	Formula, Cc.	Formula Nitrogen, Gm.	Formula Chloride, Gm.	Wangensteen Drainage, Cc.	Wangensteen Drainage Nitrogen, Gm.	Wangensteen Drainage Chloride, Gm.	Total Nitrogen Intake, Gm.	Total Nitrogen Output, Gm.	Total Chloride Intake, Gm.	Total Chloride Output, Gm.	Wangensteen Drainage Chloride, mEq.
4/11 to 4/13*	.....	....	....	...	....	....	3,440	0.98	6.08	....	0.98	....	6.08	30.2
4/13 to 4/14	.....	....	....	...	....	....	1,170	0.41	2.07	....	0.41	....	2.07	30.2
4/14 to 4/15	.....	....	....	. .	....	....	1,080	Lost	3.33	....	Lost	....	3.33	33.8
4/15 to 4/16	.....	....	....	...	....	....	2,970	0.76	4.38	....	0.76	....	4.38	25.2
4/16 to 4/17	.....	....	....	...	....	....	1,685	0.64	2.42	....	0.64	....	2.42	24.5
4/17 to 4/18	965	6.56	2.23	...	....	....	2,380	6.50	6.68	6.56	6.50	2.23	6.68	48.0
4/18 to 4/19	1,045	7.10	2.41	...	....	....	2,350	7.57	7.30	7.10	7.57	2.41	7.30	53.1
4/19 to 4/20	1,035	7.05	2.39	...	....	....	2,700	6.20	9.12	7.03	6.20	2.39	9.12	57.8
4/20 to 4/21	1,300	8.85	3.00	...	....	....	2,380	7.44	10.71	8.85	7.44	3.00	10.71	77.0
4/21 to 4/22	900	6.12	2.08	...	....	....	1,670	3.32	7.63	6.12	3.32	2.08	7.63	77.6
4/22 to 4/23	900	6.12	2.08	...	....	....	1,850	2.62	9.55	6.12	2.62	2.08	9.55	88.2
4/23 to 4/24	800	5.44	1.85	840	9.36	2.66	3,960	8.30	24.00	14.80	8.30	4.51	24.00	103.6
4/24 to 4/25	600	4.08	1.38	900	10.00	2.85	3,340	8.18	22.50	14.08	8.18	4.23	22.50	115.0
4/25 to 4/26	900	6.12	2.08	450	5.00	1.43	1,900	5.05	11.57	11.12	5.05	3.51	11.57	104.0
4/26 to 4/27	500	3.40	1.15	300	3.33	0.95	1,520	2.87	9.96	6.73	2.87	2.10	9.96	112.0
4/27 to 4/28	1,200	8.16	2.77	400	4.45	1.27	3,200	8.40	18.55	12.61	8.40	4.04	18.55	99.2
4/28 to 4/29	1,100	7.48	2.54	400	4.45	1.27	5,400	15.50	34.70	11.93	15.50	3.81	34.70	109.8
4/29 to 4/30	.....	....	....	...	....	....	3,490	3.96	18.65	....	3.96	....	18.65	91.3
4/30 to 5/ 1	.....	....	....	...	....	....	4,520	3.80	20.20	....	3.80	....	20.20	76.4

* Values obtained at 3:30 p. m. on April 11 and at noon on April 13.

withdrawn from the interstitial fluid, as the concentration in the Tyrode's solution exceeded that in the serum.[14]

Serum Chloride, Carbon Dioxide and Protein Levels (fig. 5).—Serum chlorides were easily maintained at near normal levels, apparently as the result of free exchange of ions between the blood and the Tyrode solution. The serum bicarbonate content was low at the start but rose steadily, at first as a result of administration of sodium lactate and later probably because of withdrawal of hydrochloric acid from the stomach by Wangensteen suction.

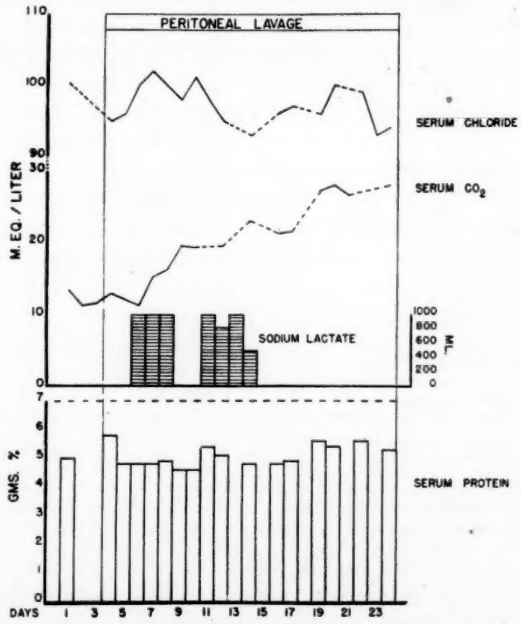

Fig. 5.—Concentration of serum chloride, carbon dioxide and protein.

A rapid fall in serum protein was anticipated when large quantities of protein were found in the drainage fluid. This did not materialize. As mentioned previously, the loss from the peritoneum was more than replaced during the first eight days by transfusions of plasma. The total loss of protein by way of the peritoneum amounted to 731 Gm. This exceeded the quantity given parenterally by about 50 Gm.

Nonprotein Nitrogen and Nitrogen Balance.—The initial fall in the concentration of nonprotein nitrogen in the blood coincided with diffu-

14. McLean, F. C., and Hastings, A. B.: Clinical Estimation and Significance of Calcium Ion Concentration in the Blood, Am. J. M. Sc. **189**:601, 1935.

sion of urea and other nitrogenous bodies into the irrigation fluid. In spite of the fact that a fairly constant amount of nitrogen (nonprotein) was removed each twenty-four hours from the fifth day until death, there was a rather abrupt rise in the level in the blood about the fourteenth day. Prior to this time, edema was severe. It began to subside as the nonprotein nitrogen level rose. Unfortunately a leak along a sinus forming about the abdominal inflow catheter happened to coincide with the period of decline in weight. This permitted some of the fluid from the reservoir to escape without traversing the peritoneal cavity. The "sump" continued to function satisfactorily, but as an accurate record of the inflow could not be obtained, no record of edema fluid which may have been lost as peritoneal transudate is available. The amount of nonprotein nitrogen removed from the fluid obtained by lavage was 6.07 Gm. a day between April 15 and 20 while the edema was intense; with loss of 14.6 Kg. in weight between April 20 and 29, the average amount of nonprotein nitrogen recovered was 6.21 Gm. a day.

The following calculation demonstrates how loss of water from the body without a corresponding loss of nitrogen could account for the increased concentrations of nonprotein nitrogen in the remaining body fluids:[15]

April 20		
Body weight	73.5 Kg.	
Blood nonprotein nitrogen	105 mg.	
Edema-free weight of body	58.9 Kg.	(as of April 29)
Nonprotein nitrogen content of body water	58.9 × 0.7 × 1.05 = 43.3 Gm.	
Nonprotein nitrogen content of edema fluid	14.6 × 1.05 = 15.3 Gm.	
Total	58.6 Gm.	
April 29		
Body weight (essentially edema free)	58.9 Kg.	
Blood nonprotein nitrogen	150 mg.	
Nonprotein nitrogen content of body water	58.9 × 0.7 × 1.50 = 61.9 Gm.	

Two avenues for the escape of water from the body were open, which in the circumstances did not permit simultaneous loss of the nitrogen of edema fluid. These were (*a*) evaporation from the skin and lungs and (*b*) withdrawal of excess fluid by gastric suction. We estimated that the amount withdrawn was 6 Kg. during the period of dehydration. Although it is maintained that nitrogen may be lost from the body in appreciable amounts by way of gastric and intestinal secretion in uremia,[16] the introduction of an amino acid solution and protein from a formula into the stomach seems to have blocked such "vicarious

15. Peters, J. P., and Bulger, H. A.: The Relation of Albuminuria to Protein Requirement in Nephritis, Arch. Int. Med. **37**:153 (Feb.) 1926.

16. Meyers, W. A.: (*a*) Obstructive Anuria: Report of a Remarkable Case, J. A. M. A. **85**:10 (July 4) 1925; (*b*) Long Standing Anuria: Certain Associated Phenomena, ibid. **86**:1198 (April 17) 1926.

elimination" effectively (table 3). The flow of nitrogen by this route was mainly into, rather than out of, the body. Had all the orally administered nitrogen absorbed during the nine day interval under discussion been retained as nonprotein nitrogen, the concentration in the blood should have increased from 105 to 217 mg. per hundred cubic centimeters.

During the last forty-eight hours, when hope for the survival of the patient had been abandoned, only non-nitrogen-containing fluids were introduced into the stomach. She drank a considerable amount of water, and fluid was withdrawn by suction at approximately hourly

TABLE 3.—*Fluid, Nitrogen and Phosphorus Recovered from the Peritoneal Cavity*

Date, 1946	Day of Lavage	Fluid Recovered, Cc.	Total Nitrogen, Gm.	Non-protein Nitrogen, Gm.	Protein Nitrogen, Gm.	Urea and Ammonia Nitrogen, Gm.	Inorganic Phosphorus, Gm.
4/10 to 4/11	1	13,060	27.52	12.75	14.77	10.35	1.164
4/11 to 4/12	2	13,140	21.75	10.29	11.46	8.77	1.051
4/12 p. m. to 4/13 a. m.	2½	10,000	13.44	6.23	7.21	4.45	0.589
4/13 to 4/15	2½ to 5	18,060	31.58	12.91	18.67	9.90	1.230
4/15 to 4/16	6	7,760	14.30	6.19	8.11	4.32	0.528
4/16 to 4/17	7	7,950	14.90	5.90	9.00	4.37	0.488
4/17 to 4/18	8	13,560	15.00	7.89	7.11	6.50	0.712
4/18 to 4/19	9	8,570	12.82	6.10	6.72	4.72	0.517
4/19 to 4/20	10	4,570	8.00	4.26	3.74	3.29	0.365
4/20 to 4/21	11	7,580	11.20	6.66	4.54	5.29	0.569
4/21 to 4/22	12	5,880	9.21	5.14	4.07	4.06	0.419
4/22 to 4/23	13	9,370	9.84	6.69	3.15	5.32	0.539
4/23 to 4/24	14	5,880	8.32	5.25	3.07	4.16	0.397
4/24 to 4/25	15	6,520	8.94	6.62	2.32	5.16	0.503
4/25 to 4/26	16	9,480	10.55	7.40	3.15	5.93	0.649
4/26 to 4/27	17	5,580	7.66	5.36	2.30	4.10	0.459
4/27 to 4/28	18	8,560	10.00	7.36	2.64	5.87	0.635
4/28 to 4/29	19	4,340	6.66	4.78	1.88	3.86	0.416
4/29 to 4/30	20	7,770	8.32	7.14	1.18	5.56	0.608
4/30 to 5/ 1	21	4,780	7.80	5.90	1.90	4.32	0.536
Totals			257.81	140.82	116.99	110.30	12.369

intervals. Except for some mucus, this fluid contained little protein. The nitrogen concentration was 113 mg. per hundred cubic centimeters on April 29 and 84 mg. on April 30. The corresponding chloride values were 91.3 and 76.4 milliequivalents respectively. It is evident that complete equilibrium with the extracellular water had not been obtained or the concentration of nonprotein nitrogen would have been nearly as great as that of the blood.[17] Owing to the large volume of

17. Martin, L.: Total Nitrogen and Non-Protein Nitrogen Partition of Gastric Juice Obtained After Histamine Stimulation, Bull. Johns Hopkins Hosp. **49**:286, 1931. Williams, J. L., and Dick, G. F.: The Excretion of Non-Protein Nitrogen Substances by the Intestine, J. A. M. A. **100**:484 (Feb. 18) 1933.

fluid withdrawn, 7.7 Gm. of nitrogen was removed on these two days. The nitrogen balance was as follows:

Nitrogen intake		
Whole blood	63.3 Gm.	
Plasma	99.6 Gm.	
"Aminoids"	76.5 Gm.	
Special formula	36.6 Gm.	
	276.0 Gm.	276.0 Gm.
Nitrogen output		
Peritoneal drainage		
(a) Nonprotein nitrogen	140.8 Gm.	
(b) Protein nitrogen	117.0 Gm.	
Gastric suction	92.5 Gm.	
Urine	4.4 Gm.	
	354.7 Gm.	354.7 Gm.
Difference (nitrogen loss)		78.7 Gm.

The over-all nitrogen balance revealed a loss to the patient of 80 to 90 Gm. of nitrogen. The values given for the intake are reasonably complete, while the output is somewhat less than it should have been because, of three stools passed, all were lost in the bed. Another avenue of elimination of nitrogen which may be important in uremia is the skin. Measurement of excretion of nitrogen by this route is difficult under the most favorable conditions and in the present circumstances was found impracticable.

It will be noted that 72.0 per cent of the total output was from the peritoneal cavity and that almost half of this amount was protein. Returns of gastric suction accounted for 26.2 per cent, of which the major part seems to have been nitrogen from unabsorbed food. Only 1.2 per cent of the nitrogen output was found in the urine. On the intake side, whole blood and plasma accounted for 59 per cent and actually represent the main source of nitrogen available to the patient. The exchanges of protein nitrogen almost balanced each other; 153 Gm. was added to the body pool by transfusion of whole blood and plasma, and 141 Gm. was removed by peritoneal lavage. Thirty-one grams of food nitrogen seems to have been absorbed, or 11.2 per cent of the intake from all sources.

COMMENT

The choice of peritoneal lavage as a therapeutic procedure presents several technical problems as well as moral issues. It is obviously unjustified if there are sound reasons for the belief that renal function can never be reestablished at a level compatible with survival. In our experience, at least, it adds greatly to the discomfort of the patient and to the mental anguish of the family and friends. We believe that it should not be attempted unless the onset of the anuria is acute and the

chance of resolution of the lesion in the kidney within two or three weeks is good. Renal decapsulation and biopsy have been tried and might be of advantage in suitable cases.[6c] One might even question whether the procedure increases the chance of survival beyond that of more conventional methods of treatment. While it is usually thought that the victim of complete anuria will succumb within eight or ten days, survivals for twenty to thirty days are not unknown.[16] In the procedure's favor are a number of animal experiments in which the survival time of nephrectomized dogs was increased over that of controls [18] and a small series of observations on rabbits that survived a lethal dose of mercuric chloride.[1e]

The technical problems presented are those of infection, nutrition, hydration and regulation of the acid-base balance.

Infection.—Cultures of the peritoneal washings revealed the presence of Bacillus aerogenes on two occasions—on the third day of irrigation and again at autopsy. On the sixteenth day of irrigation diphtheroids were recovered. Other cultures were sterile. The inclusion of antibiotics in the lavage fluid and the aseptic technic seem to be reasonable assurance against serious infection of the peritoneum. The concentration of penicillin sodium in the lavage fluid was raised from 1,660 units per liter to 3,300 units when it was found that the fluid in the outflow tube failed to inhibit growth of test organisms in vitro. Satisfactory inhibition was found at the higher concentration. The presence of fibrinous peritonitis was demonstrated at autopsy, but whether this was the result of bacterial infection or of chemical irritation is not known.

Nutrition.—Because of nausea and vomiting accompanying the uremia, oral feeding did not prove feasible. Parenteral feeding was partially successful, but the caloric intake was far from adequate, so that a large part of the energy required by the patient must have been derived from consumption of her own tissues.

Plasma Protein in the Peritoneal Washings.—The removal of large amounts of plasma protein in the peritoneal washings is something that has not been mentioned previously. Putnam [2c] found small amounts of protein in the fluid withdrawn from the peritoneal cavity after injection of isotonic solution of sodium chloride. Balazs and Rosenak [6a] recovered protein in the amount of one-third per cent in the peritoneal washings when a 4.5 per cent solution of dextrose was introduced into the abdominal cavity in a case of mercury poisoning. Iversen and Johansen [19] noted about 0.5 per cent of protein in ascitic fluid dur-

18. Abbott and Shea.[1a] Bliss and others.[1b] Rosenak and Siwon.[1h] Seligman and others.[11]

19. Iversen, P., and Johansen, E. H.: Pathogenese und Resorption von Trans- und Exudation in der Pleura, Klin. Wchnschr. 8:309, 1929.

ing the initial stages of transudation. In the experiments of Schechter and others [2d] on normal dogs, protein appeared to diffuse slowly into isotonic solution of sodium chloride introduced into the peritoneum. They felt that whatever fluid was introduced into the peritoneal cavity tended to assume the composition of the interstitial fluid, which almost certainly contains small quantities of protein.[20] The actual concentration of protein in the peritoneal washings was small and varied from about 0.7 per cent during the first days of lavage to from 0.2 to 0.25 per

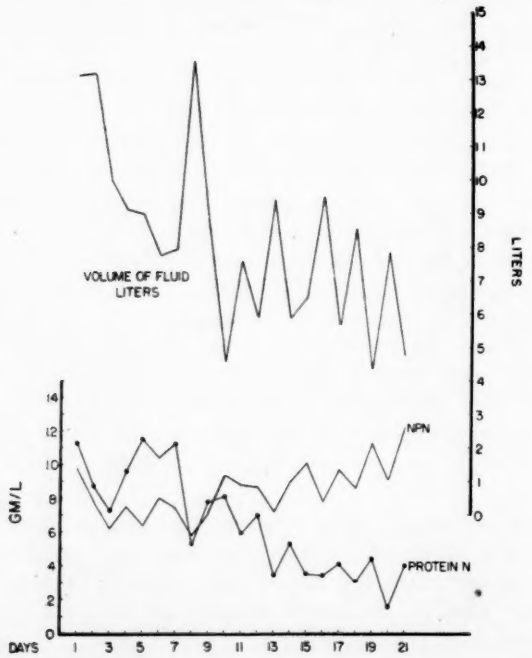

Fig. 6.—Concentration of protein nitrogen and nonprotein nitrogen as related to volume of peritoneal drainage. The concentration of protein nitrogen decreased progressively during the period of lavage, while that of nonprotein nitrogen tended to increase. An inverse relation between the volume of drainage and the concentration of nonprotein nitrogen is evident.

cent after about twelve days (fig. 6). In view of the large amount of fluid withdrawn, even this small concentration of protein resulted in a significant loss. Thus it would appear that should there be time for the fluid which is introduced to assume the characteristics of a simple

20. (*a*) Warren, J. V., and Stead, E. A., Jr.: The Protein Content of Edema Fluid in Patients with Acute Glomerulonephritis, Am. J. M. Sc. **208**:618, 1944. (b) Peters.[4]

transudate from the interstitial fluid all the protein removed could be accounted for. The opportunity for the establishment of equilibrium is favorable. The area of the peritoneal surfaces is large—about equal to that of the surface area of the body.[21] The rate of infusion of fluid did not exceed 9 cc. per minute and was usually considerably less than this. Fluid was continually withdrawn, and it is unlikely that any considerable pooling occurred. The autopsy revealed no adhesions or evidence of channeling. The fall in the concentration of protein in the washings after about eight to ten days was definite. While at autopsy there was no evidence of acute infection, it was obvious that there had been some irritation of the membranes since they were covered with a thin layer of fibrin. Possibly this coating of fibrin decreased the permeability to protein in the later stages of perfusion. Urea and inorganic phosphorus were found in the outflow in about as high a concentration as previously, which would indicate little change in permeability with regard to crystalloids. Another possibility is that the nephritic process was more acute at the start and that since acute nephritis is supposed to be associated with generally increased capillary permeability[22] more protein passed through the capillary wall. Against this supposition are the observations of Warren and Stead,[20a] who found the concentration of protein in interstitial fluid in acute nephritis no higher than in other edematous states. Nevertheless, the possibility that capillary permeability may have been greater in the early stage of the lavage process remains intriguing. To quote from Peters and others,[22c] "there can be little doubt, in view of the retinal lesions, the hypertension and other circulatory changes, that the pathological manifestations of acute nephritis are not confined to the kidney but involve the general vasculature of the body."

Hydration.—Difficulty in moving the patient interfered with frequent weighing. An approximate fluid balance is given in table 1. As it was impossible to measure the loss through the skin and lungs, a value for this was arbitrarily assigned of 1,000 cc. each day. In many instances the records of the oral intake were not accurately kept because of allowing the patient to hold cracked ice in her mouth, and no doubt the quantity often exceeded that given in the table. On April 19, the

21. Hertzler, A. E.: The Peritoneum, St. Louis, C. V. Mosby Company, 1919, vol. 1, p. 113. Wegner, G.: Chirurgische Bemerkungen über die Peritonealhöhle mit besonderer Berücksichtigung der Ovariotomie, Arch. f. klin. Chir. **20**:64, 1877.

22. (*a*) Beckmann, K.: Odemstudien, Deutsches Arch. f. klin. Med. **135**:39, 1921. (*b*) Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939. (*c*) Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VII. A Note on the Proteins in Acute Nephritis, J. Clin. Investigation **2**:97, 1932. (*d*) Van Slyke and Kugel.[11]

ninth day of peritoneal irrigation, the weight was 73.5 Kg., a gain of 3.7 Kg. from the last previous weighing on April 6. There was considerable pitting edema of the extremities and back. In order to determine whether as much fluid was being removed as was introduced into the peritoneal cavity, careful records were kept of the rate of inflow and outflow on several occasions when Tyrode's solution contained between 1 and 2 per cent dextrose:

Date	Hours	Inflow	Outflow	Difference
April 14	12	4,180 cc.	4,820 cc.	640 cc.
April 16	10½	1,840 cc.	2,600 cc.	760 cc.
April 18 to 19	24	7,660 cc.	8,570 cc.	910 cc.

In each instance considerably more fluid was removed than was put in. This agreed with the observations of Abbott and Shea [18] in dogs. Increasing the concentration of dextrose in the Tyrode solution seems to be an effective means of preventing excessive absorption of fluid from the peritoneum.

Acid-Base Balance.—The acid-base balance is shown in figure 5 and table 4. The usual fall in bicarbonate content of the plasma had occurred at the onset of uremia. The Tyrode solution which we employed contained only 0.05 per cent of sodium bicarbonate, or approximately 6 millimols per liter. Establishment of an equilibrium between the interstitial fluid and the Tyrode solution should have increased the acidosis, since it is improbable that bicarbonate would have been selectively absorbed by the peritoneum. The increasing concentration of bicarbonate in the serum must have been dependent on (*a*) administration of one-sixth molar sodium *r*-lactate solution intravenously and (*b*) removal of chloride ion from the stomach. With the application of Hartmann's formula,[23] the amount of one-sixth molar sodium *r*-lactate required to raise the plasma carbon dioxide from its initial level of 25 to 60 volumes per cent was 4,400 cc. Essentially this result was accomplished over a period of nine days by infusion of 6,300 cc. No lactate was administered during the last ten days of life, yet the plasma carbon dioxide gradually increased from 50 to 60 volumes per cent. The chloride content of the fluid aspirated from the stomach increased greatly at this time and, since it was highly acid, must have contained a considerable excess of chloride ion, thus freeing sodium to combine with bicarbonate. Since the concentration of other anions measured in the serum did not diminish in proportion to the increase in bicarbonate, an increase in total base is to be suspected. Positive evidence on this point was not obtained for lack of sodium or total base determinations. It would have been important also to have had obser-

23. Hartmann, A. F., and Senn, M. J. E.: Studies in Metabolism of Sodium r-Lactate: II. Response of Human Subjects with Acidosis to the Intravenous Injection of Sodium r-Lactate, J. Clin. Investigation **11**:337, 1932.

TABLE 4.—*Blood Chemistry*

Date, 1946	Day of Lavage	Non-protein Nitrogen, Mg.%	Blood Urea Nitrogen, Mg.%	Creatinine, Mg.%	Uric Acid, Mg.%	Chloride, mEq.	Carbon Dioxide, Vol.%	Serum Protein, Gm.%*	Inorganic Phosphorus, Mg.%	Calcium, Mg.%	Sugar, Mg.%	Cholesterol, Mg.%	Sulfadiazine, Mg.%
4/ 6	..	48	..	....	...	104	30	5.0 G	....	8.5	...	467	...
4/ 8	..	114	..	....	...	...	25	.....	....	...	...	...	...
4/ 9	..	127	..	....	...	...	26	.....	....	...	...	...	...
4/10	..	135	..	14.4	...	95	29	5.8 G	14.9	8.7	...	...	...
4/11	1	138	..	12.6	...	96	27	4.8 G	....	...	...	...	...
4/12	2	115	84	11.3	...	100	25	4.8 G	14.0	...	184	...	...
4/13	3	100	..	10.6	...	102	34	4.8 G	12.1	...	...	...	...
4/14	4	93	70	10.5	6.2	100	36	5.0 G	9.4	8.2	...	...	...
4/15	5	88	66	9.6	7.6	98	43.5	4.6 K	8.6	8.6	...	144	...
4/16	6	88	66	10.9	...	101	43	4.6 K	8.7	...	130	...	...
4/17	7	98	71	10.4	9.2	98	..	5.4 G	9.2	...	106	...	...
4/18	8	94	..	10.3	...	95	43.5	5.1 G	....	...	...	...	2.6
4/20	10	105	79	10.8	9.0	93	51	4.8 G	9.9	...	95	222	2.3
4/22	12	100	84	10.8	7.1	96	47.5	4.8 G	9.6	7.0	77	...	2.4
4/23	13	104	..	....	...	97	48	4.9 G	9.1	...	53	...	...
4/25	15	131	97	11.1	8.7	96	60.5	5.6 G	12.3	...	84	...	...
4/26	16	133	101	10.7	8.6	100	62	5.4 G	12.0	...	...	...	5.0
4/27	17	128	118	10.6	8.9	...	57	.....	12.7	...	110	...	...
4/28	18	152	124	10.9	9.5	99	..	5.6 G	....	...	100	...	...
4/29	19	150	136	....	...	93	..	.....	....	...	...	...	...
4/30	20	159	106	11.1	10.4	94	60	5.3 G	17.2	...	110	243	...
5/ 1	21	155	106	10.9	12.1	100	62	5.4 G	17.2	7.6	92	...	...

* G indicates the value when calculated from the specific gravity of the serum and K the value when calculated as total serum nitrogen minus nonprotein nitrogen multiplied by 6.25.

vations on the level of serum potassium. Only one specimen of serum was analyzed for potassium, on the sixteenth day of irrigation, when the level was 5.9 milliequivalents.

SUMMARY

Peritoneal irrigation was carried on continuously for twenty-one days in a patient with subacute glomerulonephritis who became almost completely anuric two days before the irrigation was started. Flow of urine was not reestablished, and the patient died. The total nitrogen removed by way of the peritoneal cavity was 257.8 Gm. Of this amount, 140.8 Gm. was nonprotein nitrogen and 117 Gm. protein nitrogen. The former was fractionated into urea and ammonia nitrogen 110.3 Gm. and undetermined nitrogen 30.5 Gm. Substantial reductions in the concentration of blood nonprotein nitrogen and serum inorganic phosphorus were obtained at first, but as the patient lost edema fluid, these values rose above the pretreatment levels. This is thought to have been due to a more rapid loss of water from the body than of nonprotein nitrogen, rather than to an increase in nitrogen catabolism.

Bicarbonate in the plasma increased from 25 to 60 volumes per cent because of the administration of sodium lactate solution intravenously and the withdrawal of chloride in excess of base from the stomach.

Dr. Eric L. Alling prepared the electrophoresis of plasma and urine protein and Dr. Roger Terry the pathologic report.

Note.—Since completion of the manuscript of this paper, another report on the treatment of acute anuria due to sulfadiazine has appeared.[24]

24. Doenges, J. P., and Strahan, C.: Treatment of Acute Sulfadiazine Anuria by Continuous Peritoneal Lavage, Bull. School Med., Univ. Maryland **31**:89, 1947.

EXCRETION OF NICOTINIC ACID IN TYPHOID

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THE LITERATURE contains many reports on the association of typhoid and pellagra. Bean and others,[1] in a review on secondary pellagra, assumed that in typhoid the rise in metabolism due to the prolonged fever leads to increased demands on the system of catalysts and brings about a state of deficiency. Sarma [2] in 1943 described the deficiency of nicotinic acid in patients with typhoid. Symptoms of this condition were glossitis and cerebral disturbances such as mania, confusion, delirium and melancholia. These symptoms could be relieved by treatment with nicotinic acid. Deficiency of nicotinic acid following typhoid has been observed in the Hadassah Rothschild University Hospital as well.[3] However, no laboratory investigations on the metabolism of nicotinic acid in typhoid have as yet been reported.

The study reported here was undertaken with the purpose of examining the urinary excretion of nicotinic acid in typhoid and of establishing a possible relationship between the rate of excretion of the acid and the clinical symptoms of its deficiency.

MATERIALS AND METHODS

Excretion of nicotinic acid [4] in the urine was studied in 17 cases of typhoid, in 4 of which the level of nicotinic acid in the blood was determined as well. The duration of the febrile period in these cases ranged from ten to forty-two days, with an average of twenty-five days. The first examination of the urine was performed after typhoid had been diagnosed, and frequent examinations were subsequently made during the febrile and convalescent periods.

Dr. Braun is from the Department of Medicine, Division B, Hadassah Rothschild University Hospital, and Dr. Grossowicz is from the Department of Hygiene and Bacteriology, The Hebrew University.

1. Bean, W. B.; Spies, T. D., and Blankenhorn, M. A.: Secondary Pellagra. Medicine **23**:1 (Feb.) 1944.

2. Sarma, A. V. S.: Use of Nicotinic Acid in Treatment of Typhoid Fever, J. Indian M. A. **13**:74 (Dec.) 1943.

3. Braun, K., and Kornblueth, W.: Secondary Deficiency Diseases, Acta med. orient. **2**:37 (March) 1943.

4. In this paper the term nicotinic acid is used to denote the combination of nicotinic acid and nicotinamide.

Urine was collected for twenty-four hours and pooled in a solution of acetic acid in a final approximately tenth-normal concentration. Samples of the specimens of urine were diluted twenty times with distilled water, sterilized and stored in a refrigerator till the day of examination. The amount of nicotinic acid plus nicotinamide was determined by a modification of the microbiologic method described by Lwoff and Querido (Grossowicz and Sherstinsky [5]). The growth rate of Proteus X 19 was used for the quantitative determination of both nicotinic acid and nicotinamide. One-tenth to 2 cc. of the diluted urine is needed for this improved test, in which the sensitivity lies between 0.01 and 0.1 micrograms per 10 cc. of the medium.

The blood was diluted 1:20 with distilled water, and the proteins were removed by the method of Isbell and others.[6] The nicotinic acid content of the blood was determined by the method just described, 0.5 cc. of blood being required for each examination.

Composition of the Test Diet.—During the entire febrile period our patients received the high nutritional, low residual diet customary in cases of typhoid—5 eggs, 1 liter of milk, 300 cc. of bouillon, 400 cc. of milk custard and 200 Gm. of fruit juice. Meat was added to this diet after the fever had subsided. The daily intake of fluid was approximately 3 liters.

The nicotinic acid content of this diet was determined as follows: The total daily intake of food was collected from the kitchen, homogenized and suspended in distilled water. The average daily intake of nicotinic acid was found to be 9.1 mg. This amount, though less than the allowances recommended by the United States National Research Council, which average about 15 mg. for normal adults, is sufficient to prevent pellagra or any other sign of deficiency.[7] Dann,[8] in summarizing dietary investigations among various classes of the American population, concluded that the minimal daily requirement of nicotinic acid for a man weighing 70 Kg. is less than 10 mg.

RESULTS

The normal values obtained by our method in healthy controls ranged from 1.0 to 2.5 mg. per liter per day. Johnson and others,[9] using a different microbiologic method, recorded 1.8 to 4.0 mg. per liter as normal values. Similar results have been obtained with chemical

5. Grossowicz, N., and Sherstinsky, E.: An Improved Microbiological Method for the Determination of Nicotinic Acid Based on the Use of Proteus HX19, J. Biol. Chem., to be published.

6. Isbell, H.; Wooley, J. G.; Butler, R. E., and Sebrell, W. H.: A Bacterial Assay Method for Nicotinamide and Related Substances in Blood, Urine and Spinal Fluid, J. Biol. Chem. **139**:499 (June) 1941.

7. Winters, J. C., and Leslie, R. E.: A Study of the Diet and Nutritional Status of Women in a Low Income Population Group, J. Nutrition **26**:443 (Nov.) 1943.

8. Dann, W. J.: The Human Requirement for Nicotinic Acid, Federation Proc. **3**:159 (Sept.) 1944.

9. Johnson, B. C.; Hamilton, T. S., and Mitchell, H. H.: The Excretion of Nicotinic Acid, Nicotinamide, Nicotinuric Acid and N-Methylnicotinamide by Normal Individuals, J. Biol. Chem. **159**:231 (June) 1945.

determinations of nicotinic acid in the urine (Goldsmith, 1.2 mg. per liter,[10] and Perlzweig and others, 1.0 to 3.0 mg. per liter[11]).

Sixteen of the 17 patients with typhoid showed a gradual decrease in the amount of excretion of nicotinic acid during the course of the infection. The amount excreted at the onset of the disease was normal or sometimes above the normal, the average being 2.55 mg. per liter. As the disease progressed, a steady decrease in excretion was noted, the minimal excretion being observed in the course of the convalescent period (fig. 1), during which time the average value was 0.59 mg. per liter. Excretion curves typical of the various stages of the disease are presented in figures 2 and 3. Both curves show that the initial excretion of nicotinic acid was above normal. The lowest values occur late

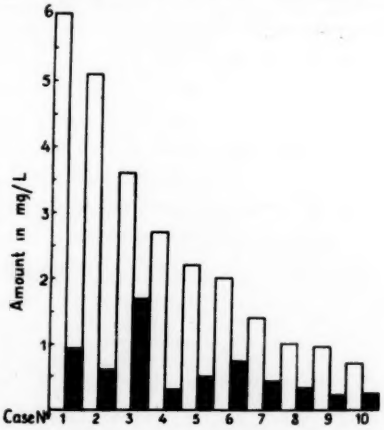

Fig. 1.—Excretion of nicotinic acid (niacin) in 10 cases of typhoid. The white columns indicate initial values and the black columns terminal values.

in the convalescent period (in figure 2 eight days and in figure 3 as late as twelve days after the fever had subsided). The effect of treatment with nicotinic acid on excretion is demonstrated in figure 2. Administration of 600 mg. daily for five days was followed by a rise in the excretion from 0.6 mg. to 5.5 mg. per liter. In only 1 of the 17 cases studied was there any considerable change in excretion. The patient in this case had mild typhoid and was admitted to the hospital three days after the onset of pyrexia. Excretion of nicotinic acid on the pa-

10. Goldsmith, G. A.: Urinary Excretion of Nicotinic Acid and Its Derivatives, Arch. Int. Med. **73**:410 (May) 1944.

11. Perlzweig, W. A.; Levy, E. D., and Sarett, H. P.: Nicotinic Acid Derivatives in Human Urine and Their Determination, J. Biol. Chem. **136**:729 (Dec.) 1940.

tient's admission was already extremely low (0.55 mg. per liter). The fever lasted for ten days only, and during convalescence the excretion fell to 0.5 mg. per liter.

In 4 patients whose blood was examined no pronounced variation in the amount of nicotinic acid were found. This is in accord with

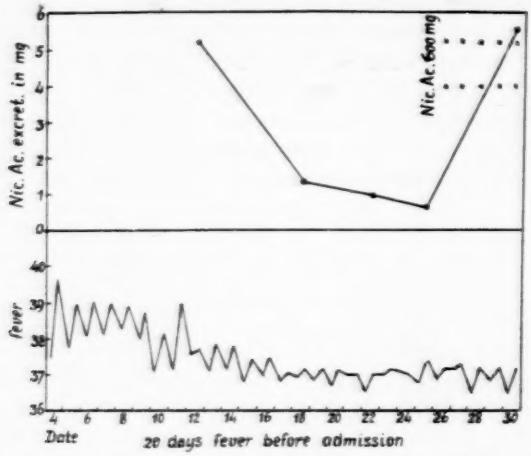

Fig. 2.—Excretion of nicotinic acid in the course of typhoid and effect of treatment on excretion.

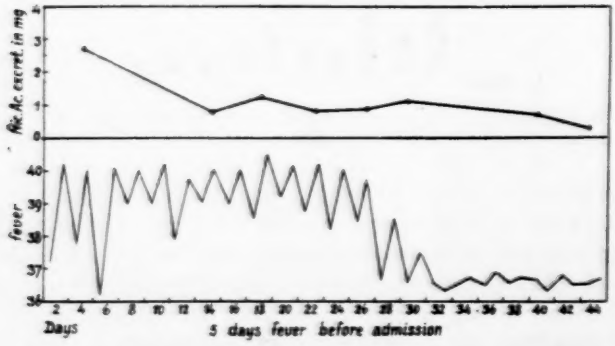

Fig. 3.—Excretion of nicotinic acid in the course of typhoid.

the results of other investigators, who observed no variations in the nicotinic acid content of the blood in various conditions, including pellagra.[12]

12. Carter, P. W., and O'Brien, J. R. P.: Nicotinic Acid Content of Blood in Health and Disease, Quart. J. Med. **14**:197 (Oct.) 1945.

Of the 16 patients with decreased excretion of nicotinic acid, 5 had glossitis as the only objective sign characteristic of deficiency. No specific clinical symptoms were observed in the other 11 patients except that they complained of general weakness, muscular pain and difficulty in concentration. These symptoms may have been due to latent vitamin deficiency, but they are indistinguishable clinically from similar symptoms attributable to the toxemia of typhoid.

COMMENT

The results reported show that there is a progressive drop in urinary excretion of nicotinic acid during the course of an attack of typhoid. The diet given to our patients contained 9.1 mg. of nicotinic acid daily, an amount sufficient to prevent deficiency.[7] Thus it seems that the diet is not responsible for the decrease in the excretion of nicotinic acid, which must therefore be attributed to intrinsic factors connected with the disease. Factors which may be implicated are: (1) diarrhea, causing loss of vitamins; (2) an inflammatory state of the intestines, interfering with the absorption and utilization of nutrients; (3) interference with the intestinal synthesis of nicotinic acid, and (4) increased vitamin requirements due to the prolonged fever.

The first possibility can be eliminated, since none of our patients had diarrhea. The second possibility cannot easily be ruled out, as the pathologic changes may be severe and may involve a large part of the small intestines and its lymphatic vessels. However, the fact that excretion of nicotinic acid was at its lowest late in the period of convalescence, when the repair of the lesions had already taken place, argues against this contention. It may be added that our patients responded to the administration of nicotinic acid with a considerable rise in excretion of the acid, indicating that absorption was not seriously impaired. Interference with intestinal synthesis of nicotinic acid is a possibility, since a disturbance in the equilibrium between the various bacteria normally present in the intestines may have occurred, leading to a decrease in the amount of nicotinic acid available.[13] The factor most likely to be responsible for the observed variations in excretion of nicotinic acid is typhoid itself, with its accompanying metabolic changes. The prolonged course of fever in typhoid is associated with an increased catabolism of foodstuffs and essential metabolites. Shaffer and Coleman [14] found a greatly increased rate of urinary excretion of nitrogen in typhoid, leading to a negative nitrogen balance. If

13. Benesch, R.: Synthesis and Destruction of Nicotinic Acid by Mixed Caecal Flora of Man, Lancet **1**:718 (June 9) 1945.

14. Shaffer, R. A., and Coleman, W.: Protein Metabolism in Typhoid Fever, Arch. Int. Med. **4**:538 (Dec.) 1909.

patients with high fever are given nutrients in amounts just sufficient to maintain normal metabolic requirements, the body is obliged to draw additional amounts from its own stores. During the early stage of the disease the body compensates for the increased demand for nicotinic acid, but as the disease progresses the stores are gradually depleted and the amount available therefore decreases. Toward the end of convalescence, when the body seems to have returned to normal, excretion of nicotinic acid is at its lowest because of the complete depletion of the body's stores.

Nicotinic acid, which as the active element of cohydrogenase is one of the essential metabolites, plays an important role in the metabolism of carbohydrates and of some amino acids. Insufficient intake of nicotinic acid in the course of the disease may therefore have a harmful effect on the functioning of various organs without leading to the full clinical picture of pellagra. These deleterious effects may, however, aggravate the course of the disease and prolong the period of convalescence.

The question arises whether the drop in excretion of nicotinic acid is due specifically to the typhoid infection or merely to the increased metabolism common to all febrile conditions of long duration. This question was not clearly elucidated in the present study for lack of an adequate number of cases of protracted pyrexia other than typhoid for comparison. A similar, though less pronounced, drop in excretion of nicotinic acid was, however, noted in 3 cases (subacute bacterial endocarditis, typhus and pneumonia). On the other hand, in 3 cases of typhus, 8 cases of pneumonia and 1 case of staphylococcic septicemia of two and a half months' duration there were no marked changes in excretion of nicotinic acid. The question of a specific relationship between typhoid and excretion of nicotinic acid therefore requires further investigation.

The increased demand for nicotinic acid demonstrated in our study justifies intensive dietary treatment and even the administration of nicotinic acid and of other synthetic vitamins. We believe that our study represents an additional contribution to recent nutritional investigations which have demonstrated the loss of nutrients during infectious disease, and which have stressed the importance of dietary treatment in shortening the period of convalescence.[15]

15. (*a*) Spies, T. D.; Vilter, R. W., and Douglas, G., Jr.: Nutrition in Convalescence and Rehabilitation; Progress Report, South. M. J. **37**:560 (Oct.) 1944. (*b*) Malnutrition During Convalescence, Prepared Under Direction of the Committee on the Convalescence and Rehabilitation of the National Research Council, War Med. **6**:1 (Jan.) 1944.

SUMMARY

Excretion of nicotinic acid in the urine was studied in 17 cases of typhoid. In 16 of these there was a gradual and progressive drop from an average maximum value of 2.55 mg. per liter at the onset to 0.59 mg. per liter during convalescence.

In only 5 of these cases did glossitis develop during convalescence, while in the other 11 there were no specific clinical signs of deficiency of nicotinic acid.

Intensive dietary treatment, with the addition of vitamins to the diet, is suggested as a preventive against vitamin deficiency.

The question of a specific relationship between typhoid and diminished excretion of nicotinic acid is discussed.

NOTE.—Since this paper was submitted for publication 8 more cases of typhoid have been examined, and values for excretion of nicotinic acid in the course of the disease were found to be similar to those reported here. Identical results were obtained from the calculation of the excretion in milligrams per liter and the calculation of the total daily urinary output of nicotinic acid in the entire 24 cases investigated.

USE OF METHIONINE AND VITAMIN SUPPLEMENTS IN TREATMENT OF HEPATIC DISEASE

Clinical and Laboratory Observations

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THE CONCEPTS of the origin and therapy of hepatic disease have changed radically in recent years. The belief that cirrhosis is caused by toxic substances, most notably alcohol, is being replaced by the concept that the primary etiologic factor is probably a dietary deficiency or that multiple etiologic agents, acting through a mechanism which produces fatty infiltration of the liver, may be responsible. This concept is supported by the experimental production of cirrhosis in animals deprived of proteins, amino acids and vitamins.

THE EXPERIMENTAL PRODUCTION AND PREVENTION OF HEPATIC DAMAGE AND CIRRHOSIS

The relationship of diet to hepatic damage in laboratory animals has been known for some time. Curtis and Newburgh produced necrosis of the liver in rats by adding as little as 0.75 per cent cystine to a diet low in casein.[1] The severity of the lesions was related to the amount of cystine used. Lillie in 1932 produced further evidence of the dietary origin of cirrhosis by demonstrating fatty degeneration of the liver in rats maintained solely on a diet low in casein.[2] In 1939 György and Goldblatt described hepatic lesions varying from fatty infiltration and fibrosis to massive necrosis in rats fed a diet deficient in vitamin B complex.[3] They were able to prevent the development of these lesions with yeast. This experiment demonstrated the fact that an agent in the

Studies on vitamin levels were done under a grant from the John and Mary R. Markle Foundation.

From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital.

1. Curtis, A. C., and Newburgh, L. H.: The Toxic Action of Cystine on Liver of Albino Rat, Arch. Int. Med. **39**:828-832 (June) 1927.

2. Lillie, R. D.: Histopathologic Changes Produced in Rats by the Addition to the Diet of Various Amino Acids, Pub. Health Rep. **47**:83-93 (Jan. 8) 1932.

3. György, P., and Goldblatt, H.: Observations on the Conditions of Dietary Hepatic Injury in Rats, J. Exper. Med. **75**:355-368 (April) 1942.

vitamin B complex was effective in preventing fatty degeneration. Best and Rideout identified the preventive factor (lipotropic principle) as choline and suggested that the accumulation of fat in the liver was due to a choline deficiency, which resulted in a decreased formation of phospholipids.[4]

Whipple and his co-workers, using dogs, had demonstrated earlier that the sensitivity of the liver to toxins was increased when the protein stores were first depleted and that the ability of the animals to withstand the effects of chloroform anesthesia was decreased.[5] They found that the sulfur-containing amino acids appeared to exert a pronounced influence in the production of hepatic damage and that they played a key role in the construction of new hepatic proteins as well as in the repair of damaged hepatic cell proteins. They searched for the fraction responsible for this favorable effect and demonstrated methionine to be the most active amino acid.

THE ACTION OF METHIONINE

Early experiments had shown that ingested protein is lipotropic and that the amount of fat found in the livers of animals fed a deficient diet was inversely proportional to the amount of protein and carbohydrate in the diet. György and Goldblatt showed that the addition of choline to a diet low in protein was helpful in the prevention of the deposition of fat and that if cystine was also added hepatic injuries could be entirely prevented.[6] Tucker and Eckstein found that methionine acted similarly to choline in the prevention of the deposition of fat in the liver.[7] Later it was found that methionine alone, when added to the diet low in protein, produced the same results as choline plus cystine and that the lipotropic activity of certain proteins was directly proportional to the amount of methionine which they contained. The lipotropic action of methionine was thought to be dependent on its ability to provide methyl groups for the formation of choline.

4. Best, C. H., and Rideout, J. H.: Choline as a Dietary Factor, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, pp. 349-370.

5. Miller, L. L.; Ross, J. F., and Whipple, G. H.: Methionine and Cystine, Specific Protein Factors Preventing Chloroform Liver Injury in Protein-Depleted Dogs, Am. J. M. Sc. **200**:739-756 (Dec.) 1940.

6. György, P.: Experimental Hepatic Injury, Am. J. Clin. Path. **14**:67-88 (Feb.) 1944.

7. Tucker, H. F., and Eckstein, H. C.: The Effect of Supplementary Methionine and Cystine on the Production of Fatty Livers by Diet, J. Biol. Chem. **121**: 479-484 (Nov.) 1937.

Du Vigneaud elaborated the hypothesis of transmethylation [8] and suggested that both cystine and choline could be made from methionine by the body and, conversely, that both acted as substitutes for methionine by utilizing the labile methyl groups present in choline. The efficacy of methionine has been shown to be the same whether it is fed as a free amino acid or as a constituent of dietary protein. Apparently the unnatural isomers of methionine can also be utilized by man equally well.[9]

Clinical Application.—Patek in 1937 published a report on the use of a nutritious diet and vitamin supplements in patients with cirrhosis.[10] This diet provided approximately 100 Gm. of protein and 300 Gm. of carbohydrate. The beneficial results noted were attributed to the regeneration of liver parenchyma and the restoration of the function of hepatic cells. Later a diet even higher in protein and supplemented by B complex vitamins and lipotropic substances was found to provide a still more effective method of treatment and often produced remissions even in cases of advanced cirrhosis.[11] Previously, when advanced disease of the liver in human beings was manifested clinically by jaundice, evidences of collateral circulation, edema or ascites the process had been considered irreversible and the prognosis extremely grave.

The efficacy of methionine in experimental hepatic damage and cirrhosis has led to its clinical trial. Beattie and Marshall reported that the administration of methionine to patients receiving arsphenamine decreased the incidence of hepatic damage.[12] The same beneficial effects have been observed in patients with acute carbon tetrachloride and trinitrotoluene poisoning. Methionine has been used in patients with infectious hepatitis and cirrhosis, with equivocal results. The limited evidence of its clinical value allows no definite conclusion to be drawn, although the encouraging results obtained appear to justify further clinical trials of methionine.[13]

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8. du Vigneaud, V.; Chandler, J. P.; Moyer, A. W., and Keppel, D. M.: The Effect of Choline on the Ability of Homocystine to Replace Methionine in the Diet, J. Biol. Chem. **131**:57-76 (Nov.) 1939.

9. Albanese, A. A.: The Utilization of *d*-Amino Acids by Man, Bull. Johns Hopkins Hosp. **75**:175-183 (Sept.) 1944.

10. Patek, A. J., Jr.: The Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329-330 (Nov.) 1937.

11. Beams, A. J.: The Treatment of Cirrhosis of the Liver with Choline and Cystine, J.A.M.A. **130**:190-194 (Jan. 26) 1946.

12. Beattie, J., and Marshall, J.: Methionine in the Treatment of Liver Damage, Nature, London **153**:525-526 (April 29) 1944.

13. The Status of Methionine in the Prevention and Treatment of Liver Injury, report of the Council on Pharmacy and Chemistry, J.A.M.A. **133**:107 (Jan. 11) 1947.

EXPERIMENTAL STUDY

Material.—In the following study 18 patients with hepatic disease received a daily oral supplement of methionine[14] in addition to the usually recommended diet. The patients were divided into three groups.

Group 1 consisted of 4 patients with acute infectious hepatitis. The diagnosis was based on the history of anorexia, malaise, vomiting and fever, the findings of enlargement and tenderness of the liver and the appearance of icterus, shown by laboratory studies to be due to parenchymatous involvement.

Group 2 consisted of 6 patients for whom the diagnosis of chronic hepatitis had been made. All gave a history resembling that of acute infectious hepatitis at the onset but continued to have persistent gastrointestinal complaints as well as clinical and laboratory evidence of hepatic damage for four to six months. Four had marked enlargement of the liver. Three continued to have jaundice of moderate or intense severity and had been treated with diet, vitamins and intravenous administration of dextrose for at least six weeks, without improvement, before the addition of methionine.

Group 3 consisted of 8 patients with chronic hepatitis and ascites (advanced portal cirrhosis of the liver). All had edema, signs of collateral circulation, jaundice and laboratory evidence of hepatic insufficiency. The clinical diagnosis was confirmed by peritoneoscopy and biopsy in 3 patients. Five patients had evidence of enlargement of the liver.

Method.—Alternate patients in groups 1 and 2 and all the patients in group 3 were hospitalized. Both the ambulatory and the hospitalized patients were given a 3,500 calory diet, made up of 120 to 140 Gm. of protein, 130 to 150 Gm. of fat and 350 to 400 Gm. of carbohydrate. Urinalysis and routine studies of the blood, including determination of the hemoglobin content, red blood cell counts, white blood cell counts and differential counts, were done. Sulfobromophthalein and hippuric acid tests and galactose tolerance tests of hepatic function were performed, and the icterus index, prothrombin time, total serum protein content and albumin and globulin fractions were determined. Plasma levels of vitamin A, carotene and ascorbic acid were measured, and the urinary excretion of riboflavin and nicotinic acid was determined. The laboratory methods used have been described in previous publications.[15]

If edema was present, the salt intake was restricted, but water was allowed ad libitum. After preliminary study, all patients received therapeutic doses of synthetic B complex vitamins and 3 to 6 Gm. of methionine each day. Hospitalized patients were also given 500 to 1,000 cc. of a 10 per cent solution of dextrose

14. The methionine was furnished by The Upjohn Company, Kalamazoo, Mich.

15. Ruffin, J. M.; Cayer, D., and Perlzweig, W. A.: The Relationship Between the Clinical Picture of a Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels, Gastroenterology **3**:340-356 (Nov.) 1944.

intravenously each day. Plasma and blood were not used. Paracentesis was done only if diuretics failed to give relief or when the accumulation of fluid produced respiratory difficulty or inability to eat. Laboratory studies were repeated every seven to ten days on all patients.

Results.—Group 1 (infectious hepatitis): In patients with acute infectious hepatitis, the duration of icterus, gastrointestinal symptoms, and disturbances of hepatic function was apparently unaltered by the methionine supplement. Since the laboratory data and clinical findings during the period of study showed no difference between the control group and those receiving methionine, the detailed results are not tabulated.

Group 2 (chronic hepatitis without ascites): Considerable improvement was noted in each of the 6 patients having chronic hepatitis without ascites (tables 1, 3 and 4). During the one month period of treatment, the values in the hippuric acid test and galactose tolerance test returned to normal. Three patients continued to show retention of sulfobromophthalein, but to a lesser degree. The total serum protein contents were unchanged. The mean plasma levels of vitamin A rose from 97 to 118 international units.

Two patients who were jaundiced had been treated in other hospitals with diet and vitamin supplements, without improvement. Within seven days after the addition of methionine, both noted an increase in appetite and subsidence of nausea, bloating and malaise. The icterus cleared rapidly. When medication was temporarily discontinued after one month, both patients stated that they could note a difference in their feelings and requested that they again be given methionine.

This group (both the ambulatory and the hospitalized patients) showed the most rapid subjective and objective response to treatment. The interval before improvement was noted was the same in the 2 patients who had received previous treatment without methionine as in the patients whose treatment was begun with methionine.

Group 3 (chronic hepatitis with ascites, or advanced portal cirrhosis): Evidences of decreased hepatic function were most notable in this group. All studies of hepatic function indicated some improvement during the period of study, although evidence of impaired function continued (tables 2 and 3). The serum protein rose from a mean of 5.3 Gm. per hundred cubic centimeters to 6.0 Gm., and a mean rise of 10 per cent in hemoglobin was also noted. The vitamin A level showed a rise of similar degree. Of the 8 patients, 7 were improved after an average treatment interval of one month (table 4). One patient who had had recurrent ascites requiring several parencenteses during the previous year was able to return to work as a railroad engineer and has remained well. In 2 patients who had jaundice as well as ascites, abdominal fluid and icterus

TABLE 1.—*Laboratory Evidence of Hepatic Damage Before and After Treatment with Methionine in Six Patients with Chronic Hepatitis (Group 2)*

TABLE 1.—*Laboratory Evidence of Hepatic Damage Before and After Treatment with Methionine in Six Patients with Chronic Hepatitis (Group 2)*

Case	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Icterus Index, Units		Hemoglobin, Gm.		Enlargement of the Liver	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	176	149	5.5	5.4	60	5	...	...	3.1	0.8	30	4	14.5	15.5	0	0
2	48	92	5.7	6.3	65	15	1.5	3.0	2.9	0.6	26	15	14.0	14.6	1+	±
3	141	142	6.5	6.5	70	0	0.64	2.95	...	...	12	8	12.8	14.0	0	0
4	78	105	7.8(?)	6.6	70	30	...	...	...	...	5	5	12.4	12.4	3+	2+
5	50	115	5.8	6.2	100	90	1.4	2.9	...	...	30	25	14.0	14.0	2+	0
6	88	103	7.1	6.4	90	0	1.7	3.0	3.8	1.3	15	10	11.2	11.0	2+	1+

TABLE 2.—*Laboratory Evidence of Hepatic Damage Before and After Treatment with Methionine in Eight Patients with Advanced Portal Cirrhosis (Group 3)*

Case	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Icterus Index, Units		Hemoglobin, Gm.		Enlargement of the Liver		Ascites	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	78	136	4.6	6.3	80	70	1.4	3.5	3.6	...	20	10	10.8	11.7	2+	1+	3+	0
2	74	82	5.2	6.1	95	40	2.7	...	1.0	1.9	9	10	12.4	11.5	1+	1+	2+	0
3	38	75	4.2	5.3	80	10	0.7	0.69	2.9	0.45	10	5	4.7	11	0	0	4+*	2+
4	77	115	6.0	5.0	95	40	1.6	1.6	1.6	1.0	20	10	12.5	14.6	1+	±	2+	0
5	125	85	5.2	5.7	80	50	...	...	...	...	10	10	9.6	9.6	1+	1+	2+*	1+
6	...	...	5.7	6.5	80	30	...	...	1.2	1.0	80	20	12.4	12.4	0	0	3+*	0
7	35	68	5.4	6.2	50	70	1.33	0.44	9.6	2.8	15	12	12.4	13.2	3+	3+	1+	1+
8	...	...	5.9	7.4	70	30	0.47†	0.38	3.04	...	10	10	10.8	....	0	0	4+	2+

* Paracenteses were performed in these cases.
† Value obtained in the intravenous test.

TABLE 3.—*Summary of Laboratory Data (Mean Values for Groups 2 and 3)*

	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Hemoglobin, Gm.	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group 2, chronic hepatitis without ascites (6 patients)	97	118	6.4	6.2	76	23.5	1.3	3.1	3.3	0.9	13.0	13.5
Group 3, chronic hepatitis with ascites (8 patients)	71	93	5.3	6.0	79	42	1.5	3.1	3.3	1.4	10.0	11.9

completely disappeared; they were able to return to full time work within two months and have remained well. Three patients showed an increase in strength and appetite together with regression of ascites but were unable to return to active work. One patient who also had arteriosclerotic heart disease with congestive failure showed no response to treatment but went progressively downhill and died. The remaining patient showed moderate improvement and returned to work, but he died after an initial massive gastrointestinal hemorrhage.

TABLE 4.—*Clinical Results*

	Group 2 Chronic Hepatitis Without Ascites (6 Patients)	Group 3 Chronic Hepatitis with Ascites (8 Patients)
Showed improvement in signs * and symptoms †	6	7
Able to resume full activities.....	6	3
Did not improve or died.....	0	2 died, 1 of massive hemorrhage after returning to work and 1 of arteriosclerotic heart disease with congestive failure and hepatic insufficiency ‡
Average duration of follow-up.....	14 mo.	13 mo.

* Decrease in edema, ascites, anorexia, size of liver and jaundice.
† Increase in appetite, strength and well-being.
‡ Death occurred after three months.

COMMENT

Diet.—The importance of a nutritious diet high in protein and carbohydrate is well recognized in the treatment of disease of the liver. Such a diet was given in multiple small feedings to all the patients in this study, and in most instances it was well and completely taken. Amino acid solutions were given to 4 patients, but the unpleasant taste of the mixtures tended to limit their oral use. No additional benefit was noted in 3 patients who received amino acids parenterally; apparently this method of administration did not provide more complete utilization or result in a greater increase in plasma protein formation. One patient who was receiving a protein hydrolysate intravenously showed a generalized erythematous follicular eruption. When severe hepatic insufficiency is present, the administration of incomplete protein digests is probably contraindicated, since they may be poorly handled by the damaged liver.

The beneficial effects of a high carbohydrate intake in patients with hepatic disease are generally accepted. It is felt that carbohydrates are important chiefly for their protein-sparing capacity. In addition, the storage of glycogen in the liver appears to limit fatty infiltration. Since glycogen is stored in damaged livers only when the blood sugar levels are high, the intravenous administration of a 5 to 10 per cent solution

of dextrose is of added value in patients unable to ingest optimal amounts of carbohydrate.

Transfusions of plasma or whole blood were not found necessary for replacement of hemoglobin and protein in the patients in this series.

Vitamin Supplements.—Since the relationship of nutrition to cirrhosis was demonstrated, it has become customary to give large amounts of B complex vitamins to patients with disease of the liver. Vitamin B complex is of great importance in the mobilization of liver lipids. Handler and Dann, however, have showed that the administration of large doses of nicotinamide to rats produces fatty livers.[16] It has also been suggested that the diseased liver may lose its ability to cope with the persistent demand for methylation.[17] Gillman noted that patients with pellagra who had fatty livers (proved by aspiration biopsy) were less likely to recover when large amounts of nicotinic acid alone were administered than when powdered stomach ("ventriculin") was given.[18]

In this study the urinary excretion of nicotinamide and riboflavin was measured before and after a test dose of these vitamins in 3 patients with cirrhosis (group 3) who had not previously received any vitamin supplements. The excretion of riboflavin was within normal limits, but the levels of nicotinamide, as measured by excretion of *N'*methylnicotinamide, were two to three times greater than normal. A high incidence of increased excretion of *N'*methylnicotinamide in patients with hepatic damage (as well as in rats poisoned with carbon tetrachloride) has also been noted by Perlzweig and his co-workers. This finding demonstrates the diminished capacity of the damaged liver to utilize and break down nicotinamide.[19]

From the information available it would appear that large doses of nicotinic acid in patients with hepatic damage might overtax the methylating ability of the liver and produce increased damage. I have preferred for this reason to use a daily vitamin supplement containing 10 to 15 mg. of nicotinamide rather than the larger amounts usually recommended (100 to 150 mg.). More detailed study of the actual

16. Handler, P., and Dann, W. J.: The Inhibition of Rat Growth by Nicotinamide, J. Biol. Chem. **146**:357-368 (Dec.) 1942.

17. Najjar, V. A.; Hall, R. S., and Deal, C. C.: The Methylation of Nicotinamide, Bull. Johns Hopkins Hosp. **76**:83-91 (Feb.) 1945.

18. Gillman, T., and others: Substitution of Whole Stomach Extract for Vitamins in Treatment of Malignant Infantile Pellagra, Nature, London **154**:210 (Aug. 12) 1944.

19. Perlzweig, W. A.; Huff, J. W., and Rosen, F.: The Effect of CCl_4 Poisoning on the Fate of *N'*Methylnicotinamide in the Rat, Federation Proc. **5**: 149 (Feb.) 1946.

vitamin needs and the degree of utilization in patients with hepatic disease is indicated.

Although many of the patients were found to have lowered plasma levels of vitamin A, the values for the most part fell in the low normal range. These comparatively low levels were probably dependent on decreased intake and absorption and on accumulation in the fatty liver. It is well recognized that in patients with hepatic disease low levels of vitamin A in the plasma may exist without signs of a frank deficiency. Nothing to indicate any clinical deficiency of vitamin A was noted in the patients in this series, and it was not felt that administration of accessory vitamin A was indicated.

In most of the patients, plasma levels of ascorbic acid were also within low normal limits, and no supplementary vitamin C was administered.

Vitamin K was given only to patients whose stools contained no bile and in whom a prothrombin deficiency could be demonstrated. In such patients the prothrombin time returned to normal within one to two days after the injection of 1 mg. of vitamin K or in two to three days if 1 mg. of vitamin K and 1 Gm. of the bile salts were administered orally each day.

Methionine.—Since methionine appears to be the amino acid most essential for normal hepatic function and since it acts to prevent the deposition of fat in the liver as well as to protect the liver against nutritional deficiencies and hepatotoxic agents, supplementary doses of methionine would seem to be justified in the treatment of patients with hepatic damage. The use of a single substance rather than a combination of choline and cystine has the advantage of simplicity and obviates any danger associated with the possible toxicity of cystine. The administration of adequate amounts of methionine by diet alone may be difficult in patients who have anorexia, since they may be unable to ingest the necessary amounts of food. Casein is the richest dietary source of methionine, but approximately 1 gallon (3.7 liters) of milk would be required to supply 3 Gm. of methionine. In addition, there is some evidence that dietary methionine is more subject to utilization for purposes other than repair of the liver.

The patients in this series were given supplements of methionine orally in doses of 3 to 6 Gm. per day, without harmful effects. The larger doses did not appear to provide any added benefits.

Methionine in Acute Infectious Hepatitis: No improvement which could be attributed directly to methionine was noted in the patients with early infectious hepatitis. This finding confirms the work of other authors, who have used as much as 7.5 Gm. of methionine daily in the

treatment of infectious hepatitis, without demonstrable benefit.[20] The duration of jaundice, the enlargement and tenderness of the liver, the gastrointestinal symptoms and the period of hospitalization were not altered.

Methionine in Chronic Hepatitis: Among the patients with chronic hepatitis, the greatest improvement was noted in those without ascites (group 2), as might be expected. All patients with chronic hepatitis without ascites showed progressive improvement and were able to return to full activity. Three of 6 patients had been hospitalized previously and had received a diet high in protein and low in fat, accessory vitamins and intravenous injections of dextrose, without improvement; all 3 showed immediate improvement after the addition of methionine to the therapy. In 2 of these 3 patients the livers were not palpable. The remaining 4 patients in this group had moderate to pronounced hepatic enlargement, which showed some regression during the period of treatment. The presence or absence of enlargement of the liver per se did not appear to affect the prognosis with the use of methionine.

The prompt and uniform clinical improvement in these patients, particularly in those who had previously been treated by accepted methods, is of considerable interest. Unfortunately, there is little in the way of controlled laboratory and clinical data on the results of the treatment of chronic hepatitis with diet, vitamins and lipotropic substances. Morrison reported a clinical study on a group of 11 patients with chronic hepatitis who received methionine and choline in addition to a diet high in proteins and in carbohydrates, vitamins and liver extract. He felt that the addition of methionine had definite therapeutic value when the results were compared with those obtained in a group of 9 patients treated earlier without lipotropic substances.[21]

Methionine in Chronic Hepatitis with Ascites: The uniformly poor prognosis in cirrhosis after ascites appears has been noted in many excellent studies of the natural history of this disease. In a series of 150 patients seen at the Mayo Clinic between 1930 and 1938 and treated with a diet high in carbohydrate and low in protein and in fat, mercurial diuretics, intravenously administered dextrose, limitation of fluids and paracenteses, 68.8 per cent did not survive a year.[22] Ratnoff and Patek, reporting on a series of 386 patients, also found that more than

20. Wilson, C.; Pollock, M. R., and Harris, A. D.: Therapeutic Trial of Methionine in Infective Hepatitis, Brit. M. J. **1**:399-401 (March 24) 1945.

21. Morrison, L. M.: The Response of Cirrhosis of Liver to an Intensive Combined Therapy, Ann. Int. Med. **24**:465-478 (March) 1946.

22. Fleming, R. G., and Snell, A. M.: Portal Cirrhosis with Ascites: An Analysis of Two Hundred Cases with Special Reference to Prognosis and Treatment, Am. J. Digest. Dis. **9**:115-120 (April) 1942.

60 per cent died within a year after the first symptoms of the disease.[23] The spontaneous loss or absorption of ascitic fluid occurred in only 7 per cent of the cases. With the use of the supplemental diet and accessory vitamins, 60 per cent showed a disappearance of ascites and 20 per cent showed signs of clinical recovery. These carefully followed studies serve as a clinical control for the cases here reported in group 3.

While it is admittedly unwise to draw conclusions from the small number of cases reported in this paper, the response of the patients with chronic hepatitis, both with and without ascites, seems worthy of note. Of 8 patients with advanced cirrhosis, 3 who had jaundice and ascites have been clinically well and able to carry on full time work for an average duration of thirteen months after treatment. Three others are still alive but are forced to restrict their activity; 1 of these requires occasional paracenteses. Both the clinical and the laboratory data, however, indicate that these 3 patients improved under treatment with methionine.

SUMMARY

During the past decade the changes in the therapy of patients with chronic disease of the liver have greatly altered the prognosis for such persons. The underlying defect in many instances appears to be the accumulation of fat in the liver cells as a result of dietary deficiencies, infection or hepatotoxins.

The use of vitamin supplements and a high calorie diet containing increased amounts of protein and carbohydrate is important in mobilizing the lipids of the liver, repairing hepatic damage and restoring hepatic function.

Experimental as well as clinical observations indicate that the administration of excessively large amounts of nicotinamide may further decrease the methylating ability of the damaged liver and is unwise in view of the diminished ability of the liver to utilize and break down this vitamin.

The efficacy of methionine in the prevention and treatment of experimental hepatic injury appears to justify its clinical use. When given orally in daily doses of 3 Gm. to the patients in this series, it appeared to be most beneficial in cases of chronic hepatitis without ascites. No beneficial effect was noted in patients with acute infectious hepatitis.

23. Ratnoff, O. D., and Patek, A. J., Jr.: Natural History of Laennec's Cirrhosis of Liver: Analysis of Three Hundred Eighty-Six Cases, Medicine **21**:207-268 (Sept.) 1942.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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IN THIS annual review[1] of recent developments in the field of syphilology emphasis is placed on subjects of greatest current imporance. In publications appearing from July 1946 to June 1947 that emphasis is on therapy, particularly with penicillin, the limitations of which are gradually becoming apparent. There also is evident a rising tide of protest against the low specificity of current serodiagnostic tests, recently brought into sharper focus by mass testing of the blood of millions of persons by Selective Service, the American Red Cross and the armed forces separation centers. Few original articles on the fundamental problems of syphilis have appeared.

NEW BOOKS

Two clinical manuals on the venereal diseases have appeared during the period covered by this review. Lomholt's book[2] is an English

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1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (*e*) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (*f*) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (*g*) Mohr, C. F.; Padget, P.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**:470 (March) 1942. (*h*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942; (*i*) **72**: 635 (Nov.) 1943. (*j*) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **74**:390 (Nov.) 1944. (*k*) Mohr, C. F.; Scott, V.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **77**:332 (March); 428 (April) 1946. Reynolds, F. W., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **78**:592 (Nov.); **78**:733 (Dec.) 1946; **79**:92 (Jan.) 1947.

2. Lomholt, S.: Venereal Diseases in General Practice, London, H. K. Lewis & Co., Ltd., 1946.

edition of the Danish textbook which has been used widely throughout the Scandinavian countries. Delayed in publication because of the German occupation of Denmark, the book now is out of date, not so much in the discussions on the clinical manifestations of syphilis as with respect to the discussions on therapy. The clinical aspects of early syphilis are well covered and beautifully illustrated; the late manifestations of the disease, aside from the benign late lesions of the skin, are conspicuously slighted. Marshall's textbook [3] is an elementary treatise designed for general practitioners and medical students. As such, it fulfils its purpose, but to those especially trained in syphilology there are readily discernible shortcomings, especially with respect to the more modern aspects of syphilotherapy.

Vonderlehr and Heller [4] are the authors of a detailed and comprehensive account of the history of the control of venereal disease and of the newer procedures employed in the fight against the genitoinfectious diseases. Each of the authors has served as chief of the Venereal Disease Division of the United States Public Health Service, and each has been intimately associated with the wartime development of venereal disease control. Their experience eminently qualifies them to write authoritatively on venereal disease control in all its many ramifications.

Moore's monograph [5] on penicillin in syphilis is the first detailed summary of the results of the nationwide cooperative study of penicillin therapy in syphilis, with which the author has been intimately associated. Nearly half of the text is devoted to fundamental information on the chemistry, pharmacology and experimental therapeutics of penicillin. The rest of the monograph discusses the clinical applications of penicillin in various phases of syphilis.

HISTORY OF SYPHILIS

Origin of the Word "Syphilis."—Fracastorius, famous poet, astronomer and physician of the Italian Renaissance, is responsible for the introduction of the word "syphilis." In his pastoral poem "Syphilis Sive Morbus Gallicus," composed some twenty years after the appearance of the disease in epidemic form on the European continent, the hero was a shepherd named "Syphilus."

Solente [6] finds Fracastorius' description of the disease so accurate and so touchingly sincere that he suggests that perhaps the poet actually was describing his own symptoms as a victim of syphilis himself. It is

3. Marshall, J.: The Venereal Diseases: A Manual for Practitioners and Students, New York, The Macmillan Company, 1946.

4. Vonderlehr, R. A., and Heller, J. R., Jr.: The Control of Venereal Disease, New York, Reynal & Hitchcock, Inc., 1946.

5. Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1946.

6. Solente, G.: Le nom de syphilis et son mystère: Essai de solution, Presse méd. **48**:663 (Oct. 5) 1946.

noted in further support of this suspicion that Fracastorius wrote two pathetic plays about the death of his children. The idea receives further support from an unknown Paduan biographer who states that "Fracastorius had a round face, black eyes and a nose that became flat from prolonged contemplation of the stars." That the poet was not born with this nasal deformity is attested by the fact that earlier portraits did not picture him thus.

Dujardin [7] seeks to trace the origin of the term syphilis back beyond the time of Fracastorius to ancient Greek mythology. According to this author, the root word was first used by Ovid, from whom Fracastorius drew heavily in writing his famous poem. Ovid related the story of Niobe, who because of her pride was turned to stone after her children (one of whom was named "Sipyle") had been killed by Apollo. Ovid himself apparently got his material from a tale of Apollodorus (140 B. C.), who in turn may have drawn his inspiration from Homer (ninth century, B. C.). Homer mentions a Mount Sipyle in Asia Minor which to those with imagination has the appearance of a woman of sorrow, her tears (mountain streams) falling on rock formations which are not unlike the bodies of dead infants at the feet of their mother. The modern spelling of the word syphilis is thought to have originated from an error on the part of Ovid's copyists.

The Origin of Syphilis.—Entering into the controversy concerning the origin of syphilis, Wiedmann [8] sides with those who believe that the disease was present in Europe long before the return of Columbus from the New World. This author finds veiled references in the writings of the ancient Greeks, Romans and Hebrews to an "unclean disease" of the genitalia which at times was confused with leprosy and the venereal nature of which apparently was not suspected. There is also evidence, he thinks, that a disease characterized by a cutaneous rash and pains in the joints was present among the inhabitants of Western Europe before the days of Columbus' voyages. To explain the sudden outbreak of virulent syphilis in Europe in the last decade of the fifteenth century, he points out that epidemics not infrequently follow in the wake of war and that in those days Europe was torn by the armies of Charles VIII.

Some of the highlights in the history of syphilis have been described by LeVan,[9] whose article gives in tabular outline the conflicting data utilized by those who support the theory of the American origin of syphilis and those who believe that the disease was present in Europe prior to the discovery of the New World.

7. Dujardin, B.: Origine du mot syphilis, Presse méd. **55**:11 (Jan. 4) 1947.

8. Wiedmann, A.: Ueber den Ursprung der Syphilis, Wien. klin. Wchnschr. **59**:281 (May 9) 1947.

9. LeVan, P.: Highlights of the History of Syphilis, J. Social Hyg. **33**:249 (June) 1947.

Syphilis and Henry VIII.—There has long been speculation among historians of the Tudor period in England as to whether Henry VIII contracted syphilis and transmitted it to his wives and descendants. Some medical authorities are inclined to think this is a plausible explanation of Henry's numerous matrimonial misfortunes in search of a male heir and base their opinion on the following facts: (1) Henry's lusty sexual appetite; (2) the extraordinary number of premature and dead children born to two of his wives (Catherine of Aragon and Anne Boleyn); (3) the suspicious frontal bossing apparent in portraits of his daughter Mary; (4) the physical, mental and moral degeneration that he displayed in early middle life; (5) the fact that his legs became "swollen and covered with festering sores, causing an unbearable stench," and (6) the draining sinus on his leg, which conceivably could have been osseous syphilis.

In an entertaining article Ellery [10] controverts these factors as indications of syphilis in the corpulent Henry. Indicating that this king's sexual promiscuity may have been overly stressed, he suggests that Henry's wives' miscarriages and stillbirths may have been due to his choosing Rh-negative women for his first two wives, that the leg ulcers may have been either varicose or osteomyelitic, that the weight of evidence is against both dementia paralytica and tabes dorsalis and that since Henry was somewhat neurasthenic his dread of disease would have led him to undergo the traditional treatment of that day, which consisted of sweating and the administration of mercury until salivation was induced.

Patterson [11] concedes several of these arguments but points out that the obstetric histories of Catherine and Anne Boleyn, both of whom had several miscarriages or stillbirths before bearing living children, are more suggestive of syphilis than Rh incompatibility and that the statistical improbability of Henry's having chosen in succession two Rh-negative mates makes this explanation unlikely. He writes: "Syphilis was rampant in Henry's day, and, knowing what we do of Henry's bedtime habits, he must have been singularly fortunate to have escaped the ubiquitous spirochaete. In fact, if Henry VIII did not have syphilis, he jolly well deserved to."

TREPONEMA PALLIDUM AND RELATED ORGANISMS

Oral Spirohchetes.—Classification and identification of spirochetes found in the oral cavity and in the respiratory tract have been based largely on their morphologic characteristics. Confusion has arisen not

10. Ellery, R. S.: Must Syphilis Still Serve? M. J. Australia **1**:391 (March 29) 1947.

11. Patterson, H. S.: Must Syphilis Still Serve? Correspondence, M. J. Australia **1**:514 (April 19) 1947.

only because many different spirochetes have been described but also because in many cases there is lack of agreement among various authors as to the proper naming and classification of the organisms studied.

Robinson and Wichelhausen [12] point out the inadequacy of the available means for identification and classification of oral spirochetes and describe a method by which "specific" antigen extracts may be prepared from cultured spirochetes. Utilizing this method with immune serums, the authors differentiate sixteen strains of morphologically and culturally identical oral spirochetes into five groups. Two strains of oral spirochetes were found which were serologically identical with the Reiter and Kazan strains but serologically different from smaller oral spirochetes and from the Nichols and Noguchi strains of T. pallidum. The Nichols and Noguchi strains were shown to be serologically related to each other but both serologically and morphologically different from the Reiter and Kazan strains and serologically different from several strains of oral spirochetes. It is still an open question whether the serologic "groups" described actually represent different species of spirochetes or whether they indicate the existence of subtypes. The first interpretation is supported by the fact that precipitin tests apparently differentiate morphologically dissimilar spirochetes and the latter by the apparent differentiation of morphologically similar organisms and by the large number of different types thus demonstrated.

Hampp [13] has made agglutination studies, using oral spirochetes including Borrelia Vincenti and cultured strains of nonpathogenic T. pallidum. Injected intravenously into rabbits, all these spirochetal organisms evoked homologous agglutinins in high titer.

EXPERIMENTAL SYPHILIS

Experimental Syphilis in Mice.—Wile [14] reports that experimental syphilis in mice inoculated with the Nichols strain of T. pallidum remains an occult infection even after four successive passages. Dark field examinations, Warthin-Starry stains and hematoxylin-eosin preparations failed to demonstrate T. pallidum or any characteristic histopathologic changes in mouse tissues which were demonstrably infectious in rabbits. After successive passages, the pooled spleens, livers and gonads of mice retained their infectiousness for rabbits longer than did the brain tissues.

12. Robinson, L. B., and Wichelhausen, R. H.: The Problem of Indentification of Oral Spirochetes and Description of a Precipitin Test for Their Serological Differentiation, Bull. Johns Hopkins Hosp. **79**:436 (Dec.) 1946.

13. Hampp, E. G.: Agglutination Studies of the Smaller Oral Treponemes, Borrelia Vincenti and Cultured Strains of Treponema Pallidum, J. Am. Dent. A. **34**:606 (May) 1947.

14. Wile, U. J.: Transmission of Experimental Syphilis from Mouse to Mouse: Absence of Spirochaeta Pallida and of Pathologic Changes in Presence of Successful Inoculation, Am. J. Syph., Gonor. & Ven. Dis. **31**:109 (March) 1947.

In a series of experiments Stratton [15] transferred brain, lymph nodes and spleen from mice infected with syphilis directly from mouse to mouse three times without an intervening host such as a rabbit being used. The infectivity of all organs was ascertained at each transfer by inoculation into the testes of rabbits. Only on the first transfer were brain and spleen tissues infectious, but from the lymph nodes virulent organisms were recovered on all transfers. In another study lymph nodes from rabbits and brains, lymph nodes and spleen from mice infected with syphilis were frozen and maintained at a temperature of —78 C. At the end of a year the lymph nodes from rabbits and the brains from mice had lost their infectivity. The virulence of lymph nodes from mice appeared to have been attenuated, but the infectivity of mouse spleen was not impaired.

Venereal Spirochetosis of Rabbits.—There is in rabbits a naturally occurring spirochetal disease, the causative agent of which, Treponema cuniculi, is morphologically indistinguishable from the spirochetes of syphilis and yaws. In this rabbit infection lesions occur principally in the genital region, and the disease is believed to be transmitted from rabbit to rabbit by sexual contact.

Under experimental conditions rabbits may also be infected with T. cuniculi by intratesticular inoculation. McLeod and Turner,[16] who have studied experimental venereal spirochetosis, found that local and generalized lesions, positive reactions to serologic tests and a degree of immunity to reinoculation with the same species of organism that resembles that of experimental syphilitic infections develop in rabbits. Lesions produced by T. cuniculi likewise respond to treatment with neoarsphenamine. Individual lesions differed strikingly from those of experimental syphilis in their lack of the degree of induration so commonly observed in this disease. Multiple minute granulomas of the parietal tunic of the testis were observed and are considered to be peculiar to the condition. Lesions of the skin and appendages occurred in great profusion in some rabbits, but these lesions also differed from the cutaneous manifestations of experimental syphilis. Histologically, the lesions were characterized by areas of infiltration of lymphocytes, monocytes and plasma cells, much as is observed in yaws and syphilis. Lesions of the bones or involvement of the cornea of the eye were not observed among over 200 rabbits experimentally infected with T. cuniculi. The popliteal lymph nodes were shown to harbor treponemes during both the active and the clinically latent stage of the disease.

15. Stratton, E. K.: Preservation of Virulence of Treponema Pallidum: Some Additional Laboratory Methods, Arch. Dermat. & Syph. **54**:25 (July) 1946.

16. McLeod, C., and Turner, T. B.: Studies on the Biologic Relationship Between the Causative Agents of Syphilis, Yaws and Venereal Spirochetosis of Rabbits: I. Observations on Treponema Cuniculi Infection in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **30**:442 (Sept.) 1946.

Comparing the experimental disease produced in the rabbit by intratesticular inoculation with T. cuniculi with the manifestations produced by similarly inoculated Treponema pallidum and Treponema pertenue, McLeod and Turner [17] report that the reactions produced in the animal host by the three species of organisms have many features in common; lesions develop in somewhat the same sequence and bear a superficial resemblance to one another, and the serologic response is much the same in the three diseases. Nevertheless, differences in the appearance of the individual lesions and in the progression of the disease were observed, and the differences between one group and another were far greater than the differences among the animals of any one group. The authors ascribe these variations to factors inherent in substantial biologic differences in the infecting organisms rather than to those inherent in the host or the environment.

SERODIAGNOSIS OF SYPHILIS

Syphilitic Reagin.—In 1938 Marrack [18] summarized the accumulated data on the chemical and physical properties of antibodies and concluded that no convincing evidence of measurable differences between antibody globulins and globulin fractions normally present in serum had been adduced. The evidence at that time seemed to indicate that the only differences were the specific reactivity of antibodies with the appropriate antigens and possibly an increased resistance of the reactive groupings to the action of proteolytic enzymes.

The recent experiments of Henriksen [19] support this conclusion. This investigator has shown that when the floccules formed by the interaction of beef heart antigen and syphilitic serum are injected into rabbits two different antibodies are produced; one is directed against the lipid antigen of the beef heart extract and the other against syphilitic antibody. Since the second antibody reacted as well with normal human serums as with strongly positive syphilitic serums, it is concluded that "the specificity of syphilitic antibody seems to be the same as that of certain normal serum globulins."

That syphilitic reagin possesses antigenic properties has also been shown by Laporte, Pérez and Hardré de Looze.[20] These investigators

17. McLeod, C., and Turner, T. B.: Studies on the Biologic Relationship Between the Causative Agents of Syphilis, Yaws and Venereal Spirochetosis of Rabbits: II. Comparison of the Experimental Disease Produced in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **30**:455 (Sept.) 1946.

18. Marrack, J. R.: The Chemistry of Antigens and Antibodies, London, His Majesty's Stationery Office, 1938.

19. Henriksen, S. D.: The Antigenic Specificity of Syphilitic Antibody Globulin, J. Immunol. **55**:153 (Feb.) 1947.

20. Laporte, R.; Pérez, J. J., and Hardré de Looze, L.: Sur les propriétés antigéniques de la réagine syphilitique, Ann. Inst. Pasteur **72**:678 (July-Aug.) 1946.

injected into rabbits the floccules obtained by the interaction of Meinicke antigen and syphilitic serum and were able to demonstrate the development in the blood of the rabbits of an antibody.

Specificity of Serologic Precipitation.—The process of serologic precipitation is customarily described as a sequence of these two phases: a rapid primary phase involving combination of antigen and antibody molecules and a slower secondary phase in which the initial molecular complexes aggregate. The second phase is manifested by the development of opalescence and by the formation and sedimentation of macroscopic particles of precipitate. It is generally agreed that the primary phase is characterized by a high degree of serologic specificity; indeed, the specificity of this phase constitutes a fundamental theorem in modern immunochemistry. There is, however, no universal agreement regarding the character of the forces which operate in the secondary phase.

Lanni,[21] in a series of precipitative mixing experiments conducted with the aid of a turbidimeter and a dark field microscope, concludes that serologic precipitation is governed largely by a highly specific mechanism except in the terminal period, when the operation of nonspecific forces becomes apparent. His findings are used as the basis for a new description of precipitation in terms of the formation and aggregation of elementary particles of specific precipitate called seromicrons.

Cholesterolized Antigens.—Anttonen [22] has made an extensive study of the results of complement fixation tests, comparing the results obtained from Wassermann antigens with the addition of a cholesterol sensitizer with those obtained without the sensitizer. He concludes that the cholesterolized antigen is significantly superior in sensitivity to compensate for the slight decrease in specificity that attends its use.

Cardiolipin Antigen.—The requisites for a satisfactory routine serologic test for syphilis as outlined by Harris, Rosenberg and Riedel [23] are that such a test be (*a*) standardized, (*b*) reproducible, (*c*) susceptible of rapid performance by a simple technic and (*d*) characterized by a high degree of sensitivity and specificity. In a preliminary evaluation of serologic tests performed with cardiolipin-lecithin antigens, the authors report "encouraging" results in all these respects. They present their data without comment since they consider them "to be insufficient evidence on which to base an opinion of adequacy."

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21. Lanni, F.: The Specificity of Serologic Precipitation, J. Exper. Med. **84**: 167 (Aug.) 1946.

22. Anttonen, V. M.: Ueber die Verstärkung der Wassermannschen Reaktion durch Zusatz verschiedener Cholesterine zum Rinder-herzantigen und über die unspezifischen serologischen Luesreaktionen, Kuopio, Oy. Kuopion Kansallinen Kirjapaino, 1945.

23. Harris, A.; Rosenberg, A. A., and Riedel, L. M.: A Microflocculation Test for Syphilis Using Cardiolipin Antigen: Preliminary Report, J. Ven. Dis. Inform. **27**:169 (July) 1946.

Kline [24] again reports favorably on the cardiolipin-lecithin antigen, which he has found to give more specific results in the microscopic slide precipitation test in nonsyphilitic patients than Eagle, Hinton, Kahn, Kline and Mazzini antigens and more sensitive results in patients with syphilis than Hinton, Kahn and Kline antigens. Evidence is presented to demonstrate a greater specificity of cardiolipin-lecithin antigen in persons with malaria and in normal persons. That this antigen is not absolutely specific for syphilitic reagin is evidenced by the occurrence of occasional positive reactions in nonsyphilitic patients and in patients with leprosy. The excellent results obtained with cardiolipin-lecithin antigen and the simplicity of the slide flocculation technic cause the author to recommend the two as a basis for a single standard serologic test for syphilis worthy of universal adoption.

Brown [25] describes a quantitative macroprecipitation test for syphilis which utilizes a purified antigen composed of cardiolipin, lecithin and cholesterol. Comparing the test with quantitative complement fixation procedures, she found it to give results that reflect the course of syphilitic infection and the response to treatment.

However good serologic tests employing cardiolipin antigens may be, their specificity is not absolute. Stout [26] reports that in both complement fixation tests and flocculation tests performed with these antigens positive reactions occur in presumably nonsyphilitic donors in cases of (1) malaria, (2) infectious mononucleosis and (3) infections of the upper respiratory tract. False positive reactions also were observed in persons presumably nonsyphilitic and with no evidence of any disease whatsoever.

Wassermann Tests on Anticomplementary Serum.—Taran [27] describes a technic which he believes permits the satisfactory performance of a Wassermann test on anticomplementary serum. The procedure is based on the saturation of the serum with undiluted complement to satisfy the "fixing" properties of the serum. The excess complement then is destroyed and a Wassermann test performed in the usual manner. With known negative and positive serums the results with this technic were the same with complement saturation as without it. With anticomplementary serums there was good correlation between

24. Kline, B. S.: Cardiolipin-Lecithin Antigen: Recent Development Toward a Single Standard Test of the Blood for Syphilis, Arch. Dermat. & Syph. **55**:514 (April) 1947.

25. Brown, R.: A Quantitative Macroprecipitation Test for Syphilis with the Cardiolipin-Lecithin-Cholesterol Antigen, Am. J. Syph., Gonor. & Ven. Dis. **31**:304 (May) 1947.

26. Stout, G. W.: Reactivity of Tests Using Cardiolipin Antigen in a Limited Number of Nonsyphilitic Cases, Am. J. Syph., Gonor. & Ven. Dis. **31**:314 (May) 1947.

27. Taran, A.: A Simple Method for Performing a Wassermann Test on Anticomplementary Serum, J. Lab. & Clin. Med. **31**:1037 (Sept.) 1946.

tests with the complement saturation method and repeated Wassermann tests on fresh serum and Kahn flocculation tests.

Serum Preservation.—Merthiolate (sodium ethylmercurithiosalicylate) is an effective preservative and decontaminant for serum specimens intended for shipment over considerable distances. The recommended concentration (1 mg. of merthiolate per cubic centimeter of serum) has been shown not to produce nonspecific reactions in sterile serums. Recently some have questioned whether the addition of merthiolate causes a decrease in serologic titer in syphilitic serums. Rein and Bossak,[28] who have studied this problem, report that the reduction in serologic titer noted in stored, merthiolated serum is due to the temperatures to which the specimens are subjected rather than to any deleterious effect of merthiolate.

Croft and Smith[29] have studied twenty bactericidal agents as preservatives for syphilitic reagin. Serum from patients with syphilis and from normal persons was tested by the Kahn procedure at various intervals over periods of two and one-half to four weeks, the specimens having been stored at room temperature. None gave greater preservation than merthiolate, which was efficacious, depending on the amount of original contamination, in concentrations of 1:1,000 and 1:10,000. A method of preserving serum for shipment by mail with merthiolate in a concentration of 1:2,500 is described. Less than 4 per cent of two hundred specimens so preserved showed any significant decrease in titer after one week, and only 7.3 per cent deteriorated significantly in three weeks. Test specificity was not affected when concentrations of merthiolate of less than 1:1,000 were used.

FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS

The problem of false positive reactions to serologic tests for syphilis, brought more and more into focus because of increasingly widespread routine use of serodiagnostic tests (especially during and since World War II, when millions of serologic tests have been performed on inductees, separatees and prospective blood donors), is a serious and vexing one. The year has seen growing discontent because of the lack of specificity inherent in the sensitive serologic tests in current use.

In general, the more sensitive the serodiagnostic test, the less specific it is. Indeed, Kahn[30] has recently rediscovered a phenomenon well

28. Rein, C. R., and Bossak, H. N.: Merthiolate (Sodium Ethyl Mercuri Thiosalicylate) as a Preservative in Sera for the Serodiagnosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:343 (July) 1946.

29. Croft, C. C., and Smith, L. L.: Preservatives for Syphilitic Serum with Special Reference to the Use of Merthiolate, J. Lab. & Clin. Med. **31**:1101 (Oct.) 1946.

30. Kahn, R. L.: Universal Serologic Reactivity with Lipid Antigens: Basis for "False Positives," Am. J. Pub. Health **37**:283 (March) 1947.

known to older serologists, which is that serologic tests for syphilis may be performed under technical conditions which will elicit positive reactions in most nonsyphilitic persons. These "universal serologic reactions" may be elicited by serum-lipid antigen combinations under a variety of conditions, low sodium chloride concentration and low temperature being especially favorable to the occurrence of a positive reaction to flocculation tests in normal persons. The sensitivity of the tests may be increased or decreased in numerous ways. Wheeler, Brandon and Kahn,[31] for example, have demonstrated antagonistic effects of cephalin and lecithin on the Kahn antigen. Cephalin was found to increase sensitivity, whereas lecithin caused a decrease, making possible "correction of antigen" in either direction. Many extraneous factors appear to influence the results of serologic procedures. The experiments of Breazeale and Dunn[32] suggest that even exposure of serum specimens to sufficient concentrations of tobacco smoke may influence the accuracy of serologic tests for syphilis. It is reported that in the presence of tobacco smoke the "titer" of syphilitic serum was increased slightly.

Miller[33] contrasts the simplicity of interpretation of the serologic tests in use thirty years ago with the difficulties inherent in the adjudication of the results of the multiplicity of the highly sensitive tests in use today. Outlining a suggested method of approach to the clinical study of false positive reaction to serologic tests, he recommends that the physician should suspect a false positive result if (1) reactions are weakly positive or doubtful, (2) there are discrepancies between the results of flocculation tests and those of complement fixation tests, (3) reactions to confirmatory tests are positive only in low titer or fluctuant in degree of positivity or (4) reactions to serologic tests become or tend to become negative within a period of three months in the absence of treatment.

Serologic Surveys.—Wolman[34] has surveyed the significance of 783 positive Kahn reactions as encountered in a population of 82,070 male enrollees in the United States Maritime Service. His study indicates that 40 per cent of these men had single positive reactions of

31. Wheeler, A. H.; Brandon, E. M., and Kahn, R. L.: The Effect of Lipids on Kahn Antigen: I. Reduction of Sensitivity by Addition of Lecithin, Am. J. Clin. Path. **17**:117 (Feb.) 1947; II. Increase of Sensitivity by the Addition of Cephalin, ibid. **17**:130 (Feb.) 1947.

32. Breazeale, E. L., and Dunn, C. W.: Effect of Tobacco Smoke on Kahn and Hinton Reactions, Arizona Med. **3**:239 (July) 1946.

33. Miller, A. L., Jr.: Biologically False-Positive Wassermann Tests in Non-Syphilitic Patients, New Orleans M. & S. J. **99**:335 (Jan.) 1947.

34. Wolman, I. J.: Positive Reaction to the Kahn Test for Syphilis: Their Incidence and Meaning in Healthy American Men; a Survey of 82,070 U. S. Maritime Service Enrollees, Am. J. M. Sc. **212**:280 (Sept.) 1946.

questionable authenticity, 13 per cent had nonsyphilitic persistently positive reactions, 7 per cent had congenital syphilis and 40 per cent had acquired syphilis. The rates for false positive reactions and the incidence of congenital syphilis were essentially constant with all age groups. The incidence of acquired syphilis progressively increased with advance in years. In this author's experience the finding of a positive or doubtful reaction to the serologic test led to a diagnosis of syphilis in 47 per cent of a group of healthy American men. Weakly positive reactions proved to mean the presence of syphilis in only 20 per cent of the group, whereas strongly positive reactions proved to mean syphilis in 80 per cent of the group.

The statistics of the Selective Service on more than fifteen million registrants reveal that approximately 5 per cent of men of military age had some form of venereal disease at the time of their physical examinations. The estimated incidence for white registrants was 2 per cent, while the incidence among Negroes was 22 per cent. Among Negroes venereal disease was the second most frequent cause for rejection.

Greve's analysis [35] of Selective Service data shows that:

1. The majority of rejections for syphilis were made on the basis of a positive serological blood test alone.

2. Syphilis was the principal cause for the rejection of 271,000, or 6.0 per cent, of those registrants in rejected classes on January 1, 1945. As of the same date there were 18,400 registrants, or 0.4 per cent of all rejected registrants, who had been rejected for gonorrhea and venereal diseases other than syphilis.

3. Approximately 5 per cent of the registrants were found to have a venereal disease at the time of physical examination.

4. The rejection rate for syphilis decreased from 24 per 1,000 examined in peacetime to 4 per 1,000 examined in 1944. The rejection rates for gonorrhea and other venereal diseases decreased from 7 to 0.3 per 1,000 registrants examined during this same period.

5. The decrease in the rejection rate was the result of changes in standards of acceptance which ultimately provided for the acceptance of registrants with all except complicated forms of venereal diseases.

6. Venereal diseases are reported more frequently among Negroes than among white registrants, and rejection rates also are consistently higher among Negro registrants.

7. The prevalence of syphilis increases with advancing age, although the ratio between the white and Negro prevalence rates decreases from a Negro rate which is 19 times the white rate in the age group 21-25 years to about 9 times the white rate among registrants 31-35 years of age.

8. Among white registrants gainfully employed, the percentage of rejections for syphilis was highest among "other service workers" and lowest among farmers and farm laborers and students, while among Negroes it was highest among domestic and protective service workers and lowest among farmers, farm managers and farm laborers.

35. Greve, C. H.: Venereal Diseases Found in Selective Service Registrants, Am. J. Pub. Health **36**:751 (July) 1946.

Shaffer [36] reports that among a group of 150 military separatees with no history of syphilis or antisyphilitic therapy and with no evidences of syphilis other than positive reactions to serologic tests at the time of separation from the armed services 43 per cent definitely proved not to have syphilis, 40 per cent continued to show conflicting serologic results and in only 17 per cent could a definitive diagnosis of syphilis be made! He recommends that a more conservative attitude be followed in the serologic diagnosis of latent syphilis when no history of the disease exists.

TABLE 1.—*Progress Report on the Cooperative Separatee Referral and Case-Finding Program of the Army, Navy, Public Health Service and State Health Departments* *

Results of Investigation	All Separatees Referred for Diagnosis or Health Department Follow-Up (Reported Through Dec. 31, 1946 with at Least Two Months for Investigation)†					
	Positive or Doubtful Reaction of the Blood No History of Treatment			With History of Treatment		
	Number	Per Cent		Number	Per Cent	
Total reported	108,960	100.0		85,724	100.0	
No disposition received	19,891	18.3		14,337	16.7	
Not examined ‡	26,146	24.0		19,207	22.4	
Total examined	62,923	57.7	100.0	52,180	60.9	100.0
Not infected and no treatment necessary	41,755		66.4	36,155		69.3
Under treatment prior to investigation	4,601		7.3	6,359		12.2
Syphilis brought to treatment	16,567		26.3	9,666		18.5
Primary	560		0.9	305		0.6
Secondary	1,219		1.9	208		0.4
Early latent	7,856		12.5	3,041		5.8
Neurosyphilis	341		0.5	167		0.3
Other stage	2,422		3.9	2,112		4.1
Unknown stage	4,169		6.6	3,833		7.3

* Source: separatee tabulations prepared by state and regional tabulating units.
† Report on Mississippi residents through December 1945 and on California, Florida, Kentucky, Louisiana and New York city residents through June 1946.
‡ Unable to locate, moved out of area, uncooperative and similar reasons.

The experience of Rosenthal and Sobel [37] is similar. Among 508 members of the armed forces with no history of syphilis who were referred to the Department of Health in New York city because of positive or doubtful reaction to the serologic test for syphilis made at separation, a diagnosis of syphilis was established in only 23 (5 per cent). Four hundred and seventy-seven (94 per cent) of those referred had had nonspecific reactions to serologic tests and were thought not to have syphilis. The diagnosis was pending in 8 persons in the group at the time of this report.

36. Shaffer, L. W.: Nonspecific Serologic Tests for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:221 (March) 1947.

37. Rosenthal, T., and Sobel, N.: Syphilis in Army Separatees, New York State J. Med. **46**:2042 (Sept. 15) 1946.

It should be pointed out that the over-all experience with mass serologic testing of separatees has not been as unfortunate as these authors suggest. The United States Public Health Service has recently made available the data as reported throughout the nation (table 1).

Asking the question "Is mass serology (sic) worth while?" Pilcher [38] protests vigorously against what he calls the "ritualistic orgy of bloodletting" of mass serologic testing. He summarizes the results of ten years of openly fighting syphilis, with serologic tests as the leading method of campaigning, as follows:

1. Public health agencies have received a great deal of publicity.
2. Public health agencies have been greatly expanded.
3. The general public has been informed and grossly misinformed about syphilis.
4. The incidence of syphilis has been decreased by a comparatively small margin.
5. An untold amount of the taxpayers' money has been spent.[39]

Among the many who have recently become increasingly concerned over the nonspecificity of current serodiagnostic tests for syphilis, none is more bitter than Barnard.[40] This author is emphatically opposed to mass blood tests as being "medically unsound, economically wasteful and socially harmful." He states further that "as a result of certain misconceptions on the import of the serologic tests many thousands of individuals have been subjected to needless treatment, indignity and mental suffering; homes have been disrupted and lives wrecked."

Porter [41] is appalled by the estimate that "in the United States there are thousands of nonsyphilitics being treated for syphilis" in view of the facts that treatment is expensive and not without danger and requires a considerable length of time to be carried out adequately. He considers the mental reactions of the patient to be of importance also—"the heartaches, shame, worries and tendency to withdraw from his usual associates." In addition to the well known causes of false positive reactions, this author has encountered "nonspecific reactions" in infections of the upper respiratory tract ("anything from a slight cold to lobar pneumonia"), pregnancy, injuries and burns in which there is destruction of tissue and "most anything that will cause a fever and for no apparent reason at all."

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38. Pilcher, J. F.: Is Mass Serology Worth While? Texas State J. Med. **47**:540 (Jan.) 1947.

39. The last two of these statements are inaccurate. The incidence of syphilis has probably actually increased in the United States since 1941, though the exact extent is not definitely known. The money spent in venereal disease control is not an "untold amount" but is instead readily measurable at about twenty millions of dollars per year (average over a ten year period).

40. Barnard, R. D.: Are Mass Presumptive Serologic Surveys Justified by the Present Statuses of Serodiagnostic Tests and of Syphilis? Ohio State M. J. **43**:249 (March) 1947.

41. Porter, J. R.: The Positive Serological Reaction Is Not a Diagnosis of Syphilis, Illinois M. J. **91**:71 (Feb.) 1947.

The causes of this general dissatisfaction, in which the reviewers share, seem both social, technical and biologic. Unquestionably the social procedure of mass blood testing has emphasized, though it has not created, the problem. From the technical standpoint, the effort of serologists over four decades to increase sensitivity has exceeded the "optimum range" (of sensitivity versus specificity) to a point at which most if not all current serologic technics are too sensitive. Many of the supposed "biologic false positive" results are indubitably due to technical error. Finally, World War II has exposed an adult population to many extraneous factors known to produce biologic false positive results—factors which usually occur in infants or children (who are not subjected to routine serologic testing), such as vaccinia and acute exanthems, or which normally are rare in the United States, such as tropical diseases.

To the reviewers it is strongly suggested that all present day serologic technics, based as they are on a nonspecific phenomenon which itself is not understood, are unsatisfactory diagnostic weapons. There is needed fundamental biologic and immunochemical research probably based on the successful, but not yet accomplished, growth of T. pallidum on artificial mediums, a by-product of which may well be the development of wholly new serologic technics and the abandonment of the current serologic cookbookery and empiricism.

Biologic False Positive Serologic Reactions: Malaria.—In a controlled study of sporozoite-induced vivax malaria, Rein and Kent [42] examined a series of 7,493 serum specimens obtained at varying intervals from 90 nonsyphilitic volunteers, using a battery of seven serodiagnostic tests for syphilis. In 57 (63.3 per cent) of the 90 infected subjects biologic false positive reactions developed with one or more of the tests during the course of the disease. In the great majority of subjects the nonspecific reaction was transitory and of low degree. Of the battery of tests employed, the highest percentage of false positive reactions was observed with the Kahn standard test and the lowest with the Hinton flocculation test. A microflocculation test with cardiolipin antigen yielded results of exceptional specificity.

Seeking to determine the extent to which malarial serums react with lipid tissue extract antigens under technical conditions favorable for the elicitation of nonsyphilitic reactions, Kahn, Wheeler and Adams [43] found that serums of malarial origin showed a greater tendency to precipitation with lipid antigens than those of nonmalarial origin.

42. Rein, C. R., and Kent, J. F.: False Positive Tests for Syphilis: A Study of Their Incidence in Sporozoite-Induced Vivax Malaria, J. A. M. A. **133**:1001 (April 5) 1947.

43. Kahn, R. L.; Wheeler, A. H., and Adams, C.: Studies on Serology of Malaria: III. Malarial Precipitation Reactions with Lipid Antigens, J. Nat. Malaria Soc. **6**:74 (March) 1947.

Vaccinia.—Tey and Tello [44] have studied the serologic reactions of 40 subjects following vaccination for smallpox. Of these, 29 were known to be nonsyphilitic, and 11 had been treated for syphilis to the point of seronegativity. Of those without syphilis, transient positive serologic reactions developed in 33 per cent, all of which were of the "general biologic" type with Kahn's "verification" test. Of the 11 known to have had syphilis, positive reactions developed in 4; one was of the "general biologic" type, two were of the syphilitic type and one was inconclusive.

Blood Donation.—During World War II, the experiences of several American Red Cross blood donor centers suggested the possibility that blood donation occasionally is a factor in the production of positive serologic reactions in nonsyphilitic donors. Three publications of significant worth on this subject were discussed in last year's review.[1e] Barnard [45] has examined the data set forth in these three publications, making certain statistical adjustments to make the three series of patients comparable. His reevaluation of the data of Boynton [46] and of Boerner, Nemser and Stokes [47] adds weight to the earlier contention of himself and his co-workers [48] that transiently false positive reactions to serologic tests for syphilis may result from phlebotomy. There is a sharp drop in the rate of seropositivity after the first blood donation, which is due to elimination of donors who initially had strongly positive reactions. There then appears to be a secondary rise in the seropositivity rate after the second donation. After this secondary rise, there is a gradual fall to zero as the number of phlebotomies per donor is increased because of the continued weeding out of "serologic reactors."

Despite these statistical contrivances there remains the possibility that the apparent increase in seropositivity rates may have been due to chance alone, as the usual significant tests for comparing percentages show no statistically valid differences. Of greater significance remains the fact that a few persons have been observed who demonstrated the sequence of initial seronegativity, confirmed seropositivity with no

44. Tey, J. A., and Tello, E. E.: Vacunación antivariólica y serorreacciones, Rev. Univ. nac. Córdoba **33**:3, 1946.

45. Barnard, R. D.: An Examination of Some Data on the Relationship of Blood Donation to False Positive Serologic Tests for Syphilis, Urol. & Cutan. Rev. **50**:406 (July) 1946.

46. Boynton, M. H.: The Incidence of Positive Serologic Reactions in Multiple Blood Donors, Am. J. Syph., Gonor. & Ven. Dis. **30**:252 (May) 1946.

47. Boerner, F.; Nemser, S., and Stokes, J. H.: A Study of the Effect of Bleeding and of Repeated Blood Donation on Serologic Tests for Syphilis, Am. J. M. Sc. **211**:571 (May) 1946.

48. Barnard, R. D.; Rein, C. R. and Doan, C. A.: False Positive Serologic Tests for Syphilis Following Blood Donation, Am. J. Syph., Gonor. & Ven. Dis. **30**:255 (May) 1946.

apparent cause other than blood donation and spontaneous reversal to seronegativity. Barnard may be entirely correct in his contention, but he has not proved it statistically.

Lupus Erythematosis.—White [49] reports the case histories of 3 patients with lupus erythematosis who despite the absence of evidences of syphilitic infection had presumably false positive reactions to serologic tests for the disease.

Brucellosis.—In the differentiation of false positive serologic reactions from those truly syphilitic, one of the most important considerations is the persistence of the positive reaction. In the majority of cases falsely positive reactions revert to negativity within a few months. Gossels [50] notes, however, that in recurrent brucellosis positive or equivocal reactions to serologic tests may occur persistently or recurrently over a period of years in the absence of syphilitic infection.

Battle Casualties.—In a study of serologic tests for syphilis performed on soldiers admitted to an evacuation hospital in France, Talmage, Dunn and Breazeale [51] report that 35 per cent of 692 persons wounded in battle had positive or doubtful reactions to serologic tests for syphilis. The highest incidence of such reactions occurred in soldiers whose wounds involved fractures and/or amputations.

Pregnancy.—In a monograph detailing the results of an extensive study of blood serologic reactions for syphilis in pregnant women Penttinen [52] concludes that pregnancy does not affect the reliability of these tests. He notes that both laboratory errors and biologic false positive reactions occur when tests are made of pregnant women, but in his experience they occur no more frequently than among other groups. Biologic false positive reactions in pregnancy occurred notably with low titers; of the strongly positive reactions, 98.8 per cent occurred in patients with syphilis. A comparison of the distribution of patients with syphilis and patients with false positive reactions in relation to the first and the latter half of pregnancy brought forth nothing to support the conjecture that the duration of pregnancy might influence the results of serologic tests for syphilis.

Injections of Penicillin.—Reassuring indeed in these days of false positive reactions to serologic tests for syphilis accompanying such

49. White, C. J.: The Problem of Positive Serologic Tests for Syphilis in Lupus Erythematosis, Am. J. Syph., Gonor. & Ven. Dis. **31**:235 (March) 1947.

50. Gossels, C. L.: Persistently Seropositive Reaction for Syphilis in Chronic Brucellosis, Virginia M. Monthly **74**:82 (Feb.) 1947.

51. Talmage, W. R.; Dunn, C. W., and Breazeale, E. L.: Effect of Battle Casualties on Serodiagnostic Tests for Syphilis, Bull. U. S. Army M. Dept. **6**:741 (Dec.) 1946.

52. Penttinen, K.: On the Wassermann and Kahn Reactions During Pregnancy, Helsinki, Mercatorin Kirjapaino, 1946.

trivial incidents as infections of the upper respiratory tract and the donation of blood is the report of Turner.[53] This author found no evidence that the addition of penicillin to serum from normal persons provoked false positive reactions, and he states the belief that the therapeutic use of penicillin can be discounted as a source of biologic false positive reactions.

Clinical Approach to Serologic Tests of Questionable Significance.—Callaway [54] has outlined the approach to questionable serologic results and includes the following requisites: (1) a careful history and physical examination; (2) repeated quantitative serologic tests; (3) repeated serologic tests in different laboratories; (4) complete studies of the blood (white blood cell count, differential studies, smears for malaria and heterophil agglutinations); (5) verification test (Neurath test "or other similar verification test"); (6) "family and contact" epidemiologic survey; (7) examination of the spinal fluid; (8) fluoroscopy of the heart and aorta, and (9) continued quantitative serologic tests to determine whether the titer is rising or falling.

"Verification" Technics.—In an attempt to devise or perfect methods for the differentiation of true syphilitic serums from biologic false positive serums, there has been at Duke University a systematic investigation of the character and properties of blood serum and serum constituents, reagin and other possible materials involved in serologic reactions. One part of this work was concerned with the electrophoretic analysis of whole serum in order (*a*) to determine the electrophoretic character of syphilitic human serum, (*b*) to seek possible characteristic differences between normal, syphilitic and biologic false positive human serums and (*c*) to provide data for relating the constitution of serum fractions to that of whole serum.

Cooper, Craig and Beard [55] made electrophoretic analyses on thirteen normal, twenty-eight syphilitic and thirty-two presumably biologic false positive human serums. They report finding significant differences between the average electrophoretic characteristics of syphilitic serums and those of serums from normal persons. These differences consisted in the presence in syphilitic serums of abnormally large relative and absolute amounts of alpha ^{1} and gamma globulins and proportionately small amounts of albumin. The quantities of alpha ^{2} and beta globulins in syphilitic serums were likewise slightly larger than those in normal serums, but the differences were not significant. Comparison of the

53. Turner, R. D.: Nonproduction by Penicillin of False Positive Reactions in Kahn and Kolmer Tests, Am. J. Clin. Path. **17**:469 (June) 1947.

54. Callaway, J. L.: The Problem of Doubtful Serologic Tests for Syphilis, South. Med. & Surg. **109**:42 (Feb.) 1947.

55. Cooper, G. R.; Craig, H. W., and Beard, J. W.: Electrophoretic Analysis of Syphilitic, Biologic False Positive, and Normal Human Sera, Am. J. Syph., Gonor. & Ven. Dis. **30**:555 (Nov.) 1946.

average component composition of the biologic false positive serums with that of normal serums showed no significant differences. No evidence of characteristic qualitative abnormalities was observed either in syphilitic serums or in biologic false positive serums, nor could the changes in syphilitic serum be related to the serologic activity of the specimens. The authors conclude that they found by means of electrophoretic analysis no basis either for the diagnosis of syphilis or for the differentiation between individual syphilitic and biologic false positive serums.

On the basis of a small series of cases Becker [56] expresses his belief that the Kahn "verification" test may be used as an adjunct to other procedures in the evaluation of questionable serologic results, although he recommends its use only for qualified syphilologists. The use of cardiolipin-lecithin antigens and of tests performed by the Neurath technic is thought "to be of even greater assistance in identification of nonspecific positive blood tests."

Repeated tests of the blood of normal and of syphilitic rabbits, in which standard serologic technics (Kolmer, Kahn and Kline) as well as the differential temperature "verification" test of Kahn were used, led Sherwood and Collins [57] to conclude that all normal rabbits have detectable amounts of reagin on one or more occasions when the tests are made repeatedly over a period of weeks. The reagin content of normal rabbits was consistently low and in only 1 animal reached as much as 8 Kahn units. Of 52 rabbits infected with syphilis and tested by Kahn's "differential temperature" technic, only 6 consistently showed the "syphilitic type" of reagin, 2 showed the "biologic type" consistently throughout the period of infection and the remaining 44 showed one or more combinations of the normal biologic, syphilitic and inconclusive types. These results seem to indicate that Kahn's differential temperature "verification" test reveals no qualitative difference between the reagin of normal animals and that of syphilitic animals but does indicate fluctuation in nonspecific factors involved in precipitation of the antigen-reagin complex.

The studies of Lubitz [58] suggest that whereas in the serum of patients with syphilis the reagin titer is unaffected by continued storage in the refrigerator the titer decreases rapidly in certain serums with false positive reactions. In this study there was no correlation between loss of titer and the initial degree of positivity. The author suggests,

56. Becker, S. W.: Practical Aspects of Verification Tests for Syphilis in Office Practice, Am. J. Syph., Gonor. & Ven. Dis. **31**:225 (March) 1947.

57. Sherwood, N. P., and Collins, C.: Experimental Syphilis: Qualitative and Quantitative Studies of Reagin in Normal and Syphilitic Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **30**:571 (Nov.) 1946.

58. Lubitz, J. M.: False Positive Kahn Reactions: Loss of Titer on Storage of Serum in Ice Box, Am. J. Clin. Path. **16**:768 (Dec.) 1946.

by way of explanation of his findings, that either the nonspecific reagin is more labile and deteriorates on standing or an inhibitor present in serum may become activated.

Other Serologic Procedures in Syphilis.—The Weltmann serum coagulation test, like the erythrocyte sedimentation test, the cephalin flocculation test and the formol-gel test, is an empiric nonspecific test used as a laboratory aid in the diagnosis of disease and in the following of its clinical course.

With respect to syphilis, the reports in the literature concerning the Weltmann serum coagulation test are conflicting. Callaway,[59] who has studied the reaction in 610 patients with syphilis, found a mild prolongation of the coagulation band in all forms of syphilis with the exception of congenital syphilis. Thirty-two patients with early syphilis received six months' treatment with metal chemotherapy, without any appreciable change in the results of the test. Neither fever therapy nor the use of penicillin altered the coagulation band of patients with neurosyphilis. There was no apparent correlation between the Weltmann reaction and the positivity or negativity of either the blood or the cerebrospinal fluid.

A novel approach to the serodiagnosis of syphilis is that proposed by Bergamasco.[60] This investigator reports that in the presence of Kahn antigen the erythrocyte sedimentation rate of patients with syphilis is significantly accelerated. He has found a fairly close correlation between the reaction in tests of this type and the Wassermann reaction. "Nonspecific" positive accelerated sedimentation rates were observed in 2 patients, 1 of whom had sarcoid and the other acute rheumatic fever.

CLINICAL MANIFESTATIONS

Early Syphilis: Primary Lesions.—From data gathered in Java before and after World War II, Simons [61] has derived certain observations on the clinical features of the primary lesion of syphilis. In 680 male patients with early syphilis this observer found the primary lesion on the glans penis in approximately half of the cases (coronal sulcus, 25 per cent; frenulum, 12.5 per cent; meatal or parameatal region, 10 per cent, and other portions of the glans, 2.5 per cent). Twenty-five per cent of chancres were on the prepuce, slightly more often on the inner surface than on the outer, 15 per cent were on the penile shaft and 10 per cent were paragenital (scrotum, pubis and thighs) or extra-

59. Callaway, J. L., and Adams, L. W.: The Weltmann Serum Coagulation Reaction in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:216 (March) 1947.

60. Bergamasco, A.: La velocita' di sedimentazione della emazie como indice di reazioni specifiche nella sifilide, Arch. ital. dermat., sif. e vener. **19**:83, 1946.

61. Simons, R. D. G. P.: Clinical Features of Over 1,200 Syphilitic Chancres and Chancroids and Over One Hundred and Forty Cases of Lymphopathia Venerea, Acta dermat.-venereol. **27**:115, 1946.

genital. There were multiple chancres in 12 per cent of the patients studied. Lesions in the coronal sulcus were most frequently firmly indurated whereas those on the shaft of the penis were least frequently. Preputial edema was noted in 7 per cent of the patients.

The frequency of occurrence of syphilitic lesions of the cervix uteri has long been known to be in proportion to the diligence with which they are sought. Guerriero, Mantooth and Moore [62] report that identification of T. pallidum by dark field examination was possible in 27 women with primary lesions of the cervix and in 14 with secondary manifestations of syphilis. For only 1 patient was a diagnosis of late syphilis established and this by biopsy rather than by visualization of the causative organism. Of significance is their observation that 90 per cent of patients with early syphilitic lesions of the cervix had other complaints such as malaise, fever, arthralgia, anorexia, serosanguineous leukorrhea or contact vaginal bleeding.

Rattner [63] reminds physicians that syphilis and scabies may occur together and that because of its inflammatory nature and unpleasant subjective symptoms scabies may obscure a coincident syphilitic infection. It is urged that caution be exercised lest lesions thought to be scabetic be dismissed as such without follow-up observations to rule out a concomitant infection with syphilis.

Secondary Manifestations: Epitrochlear Lymphadenopathy.—The epitrochlear lymph nodes are seldom palpated routinely; most often they are sought when their enlargement is expected. This practice has tended to establish the belief that all palpable epitrochlear nodes are abnormal, because their normal size and frequency of palpability are not generally appreciated. There is, in particular, a common belief that enlargement of the epitrochlear nodes is suggestive of secondary syphilis. Martin,[64] who has sought to palpate routinely the epitrochlear nodes of 200 soldiers and 100 male civilians, found that these nodes are palpable in about 40 per cent of normal persons. Among the group with palpable nodes, in 14 per cent they exceeded the size of a cherry stone. There was no evidence to support the belief that epitrochlear lymphadenopathy was more characteristic of syphilis than of other diseases.

Tonsillar Lesions.—Cohen [65] points out that the pharyngeal lesions of secondary syphilis usually are nondescript and similar to those of Vincent's infection but that syphilis should be suspected when there

62. Guerriero, W. F.; Mantooth, W. B., and Moore, W.: Syphilis of the Cervix, South. M. J. **40**:261 (March) 1947.

63. Rattner, H.: Syphilis Masked by Scabies, J. A. M. A. **131**:1241 (Aug. 10) 1946.

64. Martin, L.: Palpable Epitrochlear Glands: Incidence of Relation to Syphilis, Lancet **1**:363 (March 22) 1947.

65. Cohen, B. M.: Secondary Syphilis of the Tonsils, U. S. Nav. M. Bull. **46**:1278 (Aug.) 1946.

are bilateral, irregular and superficial denudations or ulcerations over the surfaces of the tonsils or pharynx or a thin, nonodorous, bluish white translucent membrane.

Infectiousness of Cervical Secretions.—Tello and Baggio [66] were unable to demonstrate the treponemes of syphilis in the cervical secretions of 2 women with primary syphilis or in those of 13 women with secondary manifestations in the absence of clinical lesions of the cervix.

Early Syphilitic Nephropathies.—Thomas and Schur [67] report their experiences with syphilitic nephropathies, reviewing the patients with secondary syphilis treated in the wards of the Bellevue Hospital since 1940. Twelve, or less than 0.3 per cent of those treated for secondary syphilis, had markedly abnormal urinary symptoms, which responded promptly to antisyphilitic therapy. Of the 12 cases of renal involvement, 10 were classified as cases of syphilitic nephrosis and 2 as cases of nephritis, although the authors were unable to draw any distinct line between the two conditions in some instances. In syphilitic nephrosis, results of tests of renal function usually were not significantly abnormal, but pronounced albuminuria and cylindruria were present. In early syphilitic nephritis there occurred less albuminuria and more hematuria. In 1 case of diffuse glomerulonephritis apparently due to secondary syphilis, in which there were hypertension and secondary anemia, there was response to antisyphilitic therapy with penicillin. Early syphilitic nephropathies have no demonstrable sequelae.

The possibility that subclinical involvement of the kidney may exist in early syphilis and that a focal Herxheimer reaction affecting a subclinically involved renal parenchyma may produce acute syphilitic nephrosis is suggested by Scott and Clark.[68] They have observed a patient with secondary syphilis in whom the pretreatment urinalysis had revealed nothing abnormal and in whom there developed, after penicillin therapy, the classic evidences of the nephrotic syndrome, all of which subsided spontaneously and promptly without further antisyphilitic treatment. The patient's therapy had been accompanied with a severe febrile Herxheimer reaction.

Reinfection and Relapse.—Peli,[69] after summarizing some of the European literature on the question of reinfection and superinfection

66. Tello, E. E., and Baggio, P. A.: Sifilis: La contagiosidad de las secreciones cervicales en las sifiliticas floridas, Rev. Univ. nac. Córdoba **33**:657 (May-June) 1946.

67. Thomas, E. W., and Schur, M.: Clinical Nephropathies in Early Syphilis, Arch. Int. Med. **78**:679 (Dec.) 1946.

68. Scott, V., and Clark, E. G.: Syphilitic Nephrosis as a Manifestation of a Renal Herxheimer Reaction Following Penicillin Therapy for Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **30**:463 (Sept.) 1946.

69. Peli, G.: Reinfezione e superinfezione sifilitica, Arch. ital. dermat., sif. e vener. **19**:290, 1946.

in syphilis, reports on 5 patients who were, in his opinion, reinfected and on 1 patient thought to have sustained a superinfection. All the patients had been treated with arsenicals and bismuth.

Discussing the question of "cure" of syphilis, Bohnstedt [70] reports 21 cases of reinfection with syphilis after therapy with arsphenamine and bismuth. His criteria for reinfection are: (1) the diagnosis of both the first and the second infection must be proved by dark field examination and serologic evidence; (2) the first infection must have been "adequately" treated and seronegativity attained; (3) the second infection must be manifested by a primary lesion. In the presence of secondary manifestations the differentiation between relapse and reinfection cannot be made; (4) the location of the second chancre must be different from that in the first infection, and (5) the possibility of a second exposure to a sexual partner with infectious lesions must be demonstrated.

Musing over the problem of relapse versus reinfection, Leider [71] concludes that syphilis of the prearsenotherapy era could not have been attended with reinfection, since even if symptomatic or bacteriologic cure occurred only superinfection and reactivation of the disease process were possible because of the immunoallergic state. Syphilis of the era of traditional arsenotherapy rarely was attended with reinfection. The determination of the fact of reinfection could seldom be made because of its similarity to the commoner phenomena of relapse, superinfection and reactivation of the disease process. Syphilis of the present and of the near future is, and will be, characterized by more frequent reinfection. The prospects of more frequent reinfections will significantly influence the technics of venereal disease control.

Latent Syphilis.—Jordon and Dolce [72] present data obtained on 169 patients with latent syphilis observed for ten years or more. The patients were divided into two groups on the basis of the total amount of treatment received. Group I, those "poorly treated," consisted of 69 patients who received either no treatment or less than forty injections, and group II, considered "well treated," consisted of 100 patients who received forty or more injections of an arsenical and a heavy metal either alone or in combination.

Between 20 and 25 per cent of those "poorly treated" had some late complication, most often cardiovascular involvement. The incidence

70. Bohnstedt, R. M.: Reinfektion bei Syphilis, Ztschr. f. Haut- u. Geschlechtskr. **11**:325 (June) 1947.

71. Leider, M.: Semantic Confusion and Resolution in the Concepts of Cure in Syphilis and of Reinfection with Syphilis, Am. J. Syph., Gonor. & Ven Dis. **30**:344 (July) 1946.

72. Jordon, J. W., and Dolce, F. A.: Latent Syphilis: Study of One Hundred and Sixty-Nine Cases Observed Ten Years or More, Arch. Dermat. & Syph. **54**:1 (July) 1946.

of progression appeared to be significantly higher among patients whose reactions to the serologic tests remained strongly positive after therapy. There was no evidence that an extensive early tissue reaction improved the ultimate prognosis.

In the group of 100 patients who received more than a total of forty injections of antisyphilitic drugs complications developed in only 4. There appeared to be no relationship between the incidence of complications and the serologic status, and seroresistance did not seem to detract from the prognosis. Arsenical drugs appeared to be more efficacious in the prevention of late complications than heavy metals.

The authors were unable to determine from their studies the optimum amount of antisyphilitic therapy for patients with latent syphilis, but they state the belief that forty or sixty injections are adequate. Since the highest percentage of complications occurred in patients receiving little arsenical therapy and since the outcome appeared to be only slightly influenced by prolonged heavy metal therapy, the authors believe that more emphasis should be placed on the use of arsenical therapy in patients with latent syphilis.

The management and treatment of patients with latent syphilis and of those with late symptomatic syphilis have been discussed in general terms by McElligott.[73] This author decries the use of routine schedules of therapy and stresses the fact that the management of patients should be individualized. The objects of treatment should be (1) the healing of lesions and the relief of symptoms if these are present, (2) the prevention of progression or relapse and (3) serologic reversal (least important of all). Stressing the maxim that "syphilis must not be allowed to spoil lives," he notes that although inadequate therapy may do this unnecessarily prolonged treatment may have the same result.

Late Syphilis: Syphilis of the Breast.—Kampmeier [74] indicates that when syphilitic lesions of the breast are solitary they may readily be confused with other conditions. To illustrate the point, he reports the case history of a 60 year old white woman with a chancre of the nipple and that of a 30 year old Negro woman with a gumma of the breast. Gummatous mastitis is to be differentiated from carcinoma. Most often this differentiation is made pathologically after mastectomy.

Syphilis of the Liver.—Symmers and Spain [75] report that over a period of thirty years hepar lobatum was encountered one hundred and two times among 23,792 necropsies at Bellevue Hospital. Accord-

73. McElligott, G. L. M.: The Management and Treatment of the Late and Latent Syphilitic, Brit. J. Ven. Dis. **22**:171 (Dec.) 1946.

74. Kampmeier, R. H.: Syphilis of the Breast: Chancre and Gumma, Am. Practitioner **1**:395 (March) 1947.

75. Symmers, D., and Spain, D. M.: Hepar Lobatum: Clinical Significance of the Anatomic Changes, Arch. Path. **42**:65 (July) 1946.

ing to the clinical records of 28 cases that were available for analysis, the lesion occurred in 23 men and in 5 women; 24 patients were white and 4 were Negroes, and the average age was 38.5 years. A clinical diagnosis of hepatic syphilis had been made in only 3 cases. In 18 cases the liver was palpable; in 6 instances it was nodular, and in 10 tenderness was present. The spleen was palpable in 13 cases. Jaundice occurred in 8 cases, ascites in 18, hematemesis in 7 and irregular fever in 12. The authors stress the paucity of symptoms and the relative frequency of physical signs.

Syphilis of the Lung.—Involvement of the lung is a rare manifestation of acquired syphilis, and there is considerable difference of opinion regarding its diagnosis and incidence. The controversy is attributable to the relative nonspecific clinical features, to the variation in diagnostic criteria employed and to the fact that the true nature of the lesion may be overlooked because of its obscure nature and the presence of secondary infection.

Wilson,[76] who has recently reviewed the subject of pulmonary syphilis, states that the clinical and roentgenologic manifestations of syphilis of the lung are those of any chronic pulmonary infection and most often simulate the manifestations of pulmonary tuberculosis. This author, in reporting a case with the postmortem findings, including the demonstration of spirochetes in stained section, states the belief that "the reported incidence of pulmonary syphilis would rise if this diagnosis would be considered more frequently in the presence of chronic progressive pulmonary infection associated with a positive serologic reaction and other stigmas of syphilis." Whether the expected rise in the reported incidence in these circumstances would be justifiable is, in the opinion of the reviewers, another matter.

The clinical, radiologic and pathologic aspects of acquired pulmonary syphilis were discussed by Kulchar and Windholz.[77] In these authors' expressed opinion the rarity of pulmonary syphilis, its tendency to imitate other diseases and the low index of suspicion among physicians all are factors responsible for the failure to recognize clinically late syphilis of the lung. Four cases of possible late pulmonary syphilis are reported, in none of which the diagnosis was established on more than presumptive evidence.

Paroxysmal Hemoglobinuria.—Paroxysmal cold hemoglobinuria is a phenomenon almost always associated with syphilitic infection. Wag-

76. Wilson, J. M.: Acquired Syphilis of the Lung: Report of a Case with Autopsy Findings and Demonstration of Spirochetes, Ann. Int. Med. **25**:134 (July) 1946.

77. Kulchar, G. V., and Windholz, F.: The Clinical, Radiologic and Pathologic Aspects of Late Pulmonary Syphilis: Effects of Penicillin Therapy, Am. J. Syph., Gonor. & Ven. Dis. **31**:166 (March) 1947.

ley, Zinkham and Siebens [78] have found evidence that the serum hemolysin is activated by carbon dioxide and inhibited by sulfanilamide and cyanide, two substances which inhibit the activity of carbonic anhydrase. The inhibitory effect was shown to be reversible.

In the case of paroxysmal hemoglobinuria reported by Goldberg [79] treatment with 3,600,000 units of penicillin did not prevent the occurrence of port wine–colored urine after exposure of the patient to a temperature of 40 F. although some of the constitutional symptoms were at least temporarily ameliorated.

Cardiovascular Syphilis: Isolation of T. Pallidum From the Aorta.—Hu and his fellow workers [80] have isolated virulent T. pallidum from the aorta of a Chinese rickshaw puller who died of syphilitic aortitis with aortic regurgitation. The aortic tissue was inoculated intratesticularly into a rabbit thirty-two hours after the death of the patient. Viable organisms also were isolated from juxta-articular nodules but not from the circulating blood or from the mitral valve. The patient died twenty-five years after acquiring syphilis without ever receiving specific antisyphilitic treatment. This is, as far as the authors could ascertain, the first time that viable pathogenic treponemes have been shown to be present in the walls of the diseased aorta. The fact that virulent T. pallidum can be isolated from cadavers several hours after death is of practical importance to the pathologist from the standpoint of possible accidental infection at autopsy.

Diagnosis of Cardiovascular Syphilis.—Lucia and Sears [81] report that in a group of 355 patients observed in a special clinic for the treatment of cardiovascular syphilis the age distribution of the patients examined was such that hypertensive and arteriosclerotic changes made the diagnosis of uncomplicated syphilitic aortitis practically impossible and the diagnosis of syphilitic aortic regurgitation frequently difficult.

Prevention of Cardiovascular Syphilis.—Maynard and Lingg [82] present additional evidence that the administration of antisyphilitic therapy to patients with early or latent syphilis affords protection against the later development of cardiovascular involvement. Their data are based

78. Wagley, P. F.; Zinkham, W. H., and Siebens, A. A.: A Note on Studies of Hemolysis in Paroxysmal (Cold) Hemoglobinuria, Am. J. Med. **2**:342 (April) 1947.

79. Goldberg, L. C.: Treatment of Paroxysmal Hemoglobinuria with Penicillin: Report of a Case, Am. J. Syph., Gonor. & Ven. Dis. **31**:163 (March) 1947.

80. Hu, C. K.; Liu, Y.; Chen, K. C., and Frazier, C. N.: Isolation of Virulent Treponema Pallidum from Human Aorta Thirty-Two Hours After Death from Cardiovascular Syphilis, Am. J. Med. **1**:301 (Sept.) 1947.

81. Lucia, S. P., and Sears, N. N.: Diagnostic Problems in Luetic Cardiovascular Disease, California Med. **65**:207 (Nov.) 1946.

82. Maynard, E. P., Jr., and Lingg, C.: The Prevention of Cardiovascular Syphilis, Brooklyn Hosp. J. **4**:18 (July) 1946.

on approximately 600 patients studied over a period of years at the Brooklyn Hospital. Patients with hypertension, rheumatic fever, hyperthyroidism and unexplained cardiac enlargement were excluded. Their criteria for the diagnosis of uncomplicated syphilitic aortitis were: (1) the patient must have had syphilis beyond a reasonable doubt; (2) there must be no evidence of any other disease that might dilate the aorta; (3) the patient must be 40 years of age or younger; (4) there must be roentgenographic or fluoroscopic evidence of aortic dilatation; (5) there may be a hollow, accentuated aortic second sound, and (6) there may be a systolic murmur at the aortic area. The validity of these criteria was tested by a comparison of the clinical diagnosis with the observations at autopsy and by an analysis of the group to discover in how many patients more advanced lesions of cardiovascular syphilis developed.

Cardiovascular syphilis developed five times as often among patients receiving no treatment or practically none as among those to whom "adequate" courses of metal chemotherapy had been given. The incidence of syphilitic heart disease decreased as the amount of antisyphilitic therapy increased. When treatment was administered for six or more years after the appearance of the chancre evidence of cardiac involvement developed four times as often as when the treatment was completed within three years from the onset of the disease. Aortic regurgitation and aneurysm appeared much more frequently among those who had received little or no antisyphilitic therapy.

Aneurysm.—The clinical and roentgenologic features of aneurysm of the descending thoracic aorta are discussed by Lowenberg and Baer.[83] These authors mention the gastrointestinal syndromes produced by this lesion and emphasize the anatomic relationship of the aorta to the esophagus, which may be displaced by aneurysms in this location. Deviation of the esophagus anteriorly and to the left occurs with aneurysms at the diaphragmatic hiatus. The only other lesion commonly producing this picture is a congenital anomaly—the right-sided aortic arch. Erosion of the lower thoracic vertebrae is considered to be another characteristic sign of aneurysm of the lower thoracic aorta.

Lang [84] discusses the value of roentgenography in the diagnosis of abdominal aortic aneurysm. Calcification within the aneurysmal wall he believes to be more frequent in arteriosclerotic than in syphilitic aneurysms. A pathognomonic roentgenographic sign is pressure erosion of the vertebral bodies, which tend to assume a scalloped appearance

83. Lowenberg, S. A., and Baer, S.: Aneurysm of the Descending Thoracic Aorta, Am. Heart J. **32**:653 (Nov.) 1946.

84. Lang, E. F.: X-Ray in the Diagnosis of Abdominal Aortic Aneurysm, Harper Hosp. Bull. **5**:21 (April) 1947.

because of greater destruction of the vertebral bodies than of the elastic intervertebral disks, which resist erosion. Because of the anatomic position of the aorta, erosion usually is seen earliest in the left anterolateral position of the body. A more heroic method of diagnosis is by arteriography, with injection of the contrast medium above the lesion following catheterization of the femoral artery. The roentgen appearance after rupture varies with the degree and the site of bleeding. The commonest site of rupture is into the retroperitoneal space, and the roentgenograms show obliteration of details of the psoas muscle on the side of the rupture, with a considerable increase in density as compared to the other side. A similar increase in density with obliteration of the shadow of the psoas muscle occurs with perinephric abscess. Pressure of the hematoma on the structures at the hilus of the kidney may produce hydronephrosis and uremia. Hemorrhage also may occur around an enclosed or fixed portion of the gastrointestinal tract, such as the duodenum, and pressure from the mass of blood may cause obstruction of the intestinal lumen.

The surgical treatment of aneurysms of the abdominal aorta is none too satisfactory, primarily because of the meager collateral circulation which exists. That gradual closure of the aorta, especially at its lower end just above the iliac bifurcation, may be tolerated, however, is evidenced by the goodly number of patients in whom saddle thrombosis develops slowly at the site of atheromatous plaques. The collateral circulation requires the integrity of the iliac arteries.

The defect common to surgical methods producing aortic occlusion from the outside is that with compression there is death of the vessel wall. These degenerative lesions of the aorta, especially in the presence of hypertension, tend to make complete ligature intolerable for any length of time. Possible alternative methods of therapy are the production of gradual fibrosis with nonconstricting applications of cellophane followed later by wiring, complete excision of the sac with transections of the aorta or a combination of proximal banding with partial cellophane wrapping.

DeTakats and Reynolds [85] have observed a group of 8 patients with aneurysms of the abdominal aorta. Of these, 2 were not subjected to operation, and 2 were merely examined surgically; one aneurysm was wired, and three were banded with cellophane. Among these patients only the 3 treated with cellophane wrapping survived for any length of time.

Neurosyphilis: Asymptomatic Neurosyphilis.—Hahn and Clark [86] have reviewed the literature concerning asymptomatic neurosyphilis

85. deTakats, G., and Reynolds, J. T.: The Surgical Treatment of Aneurysms of the Abdominal Aorta, Surgery **21**:443 (April) 1947.

86. Hahn, R. D., and Clark, E. G.: Asymptomatic Neurosyphilis: A Review of the Literature, Am. J. Syph., Gonor. & Ven. Dis. **30**:305 (July) 1946.

and have found it concerned largely with the two major interrelated problems of incidence and prognosis. Critically assessing the available studies, these authors found that deficiencies were so numerous that they vitiated almost completely their value as a practical guide to therapy and prognosis in the individual case. These deficiencies fall into one or more of the following categories: insufficient number of cases, insufficient observation period, faulty statistical analysis or failure to take into consideration one or many of the variables concerned. These variables include age, race and sex of the patient, duration of infection at the time of examination of the cerebrospinal fluid, treatment received prior to the first positive reaction of the spinal fluid, degree of positivity of the reaction of the spinal fluid and the type and amount of therapy received after the diagnosis of asymptomatic neurosyphilis has been established.

In another paper Hahn and Clark [87] sought to determine the prognosis of asymptomatic neurosyphilis, with attempted consideration for the first time of the variables just mentioned. Their clinical material consisted of 533 patients who had at least two examinations of the spinal fluid and 467 patients who had at least two physical examinations. The observation period was less than two years in approximately 40 per cent and more than five years in approximately 35 per cent of the patients.

Race and sex appeared to be of slight importance in the prognosis of asymptomatic neurosyphilis. As to age, the younger the patient and the more recently acquired the syphilitic infection, the more favorable was the prognosis during the first ten years of observation. The more strongly positive the reaction of the spinal fluid on initial examination, the more unfavorable was the final condition of the spinal fluid and the greater was the probability of the development of clinical neurosyphilis. The final outcome in the spinal fluid was significantly better and the probability of the development of clinical neurosyphilis by the tenth year of observation significantly less for patients with early asymptomatic neurosyphilis (duration of syphilis, less than two years) than for patients with late asymptomatic neurosyphilis despite less intensive treatment in the former group.

The longer the period of observation, the greater was the percentage of patients in whom the reaction of the spinal fluid became negative, and the greater also was the probability of the development of clinical neurosyphilis. This seeming paradox is explained on the basis of the fact that the two groups were composed largely of patients who followed divergent paths. Progression of the spinal fluid to positivity was found to be an ominous prognostic sign.

87. Hahn, R. D.; Clark, E. G., and others: Asymptomatic Neurosyphilis: Prognosis, Am. J. Syph., Gonor. & Ven. Dis. **30**:513 (Nov.) 1946.

A direct comparison of the results of the several types of treatment was not feasible because the supplementary forms of treatment (tryparsamide, malarial therapy) were more frequently given to patients with the more resistant spinal fluids. It was possible, however, to demonstrate in some cases the relatively benign nature of spinal fluid which reacted positively as well as the value of routine chemotherapy in many cases. The incidence of clinical progression over a ten year period in untreated asymptomatic neurosyphilis was estimated at approximately 20 per cent. There was no evidence that the addition of tryparsamide was of value in the treatment of asymptomatic neurosyphilis.

Malarial therapy was given to a relatively small group of patients, over one half of whom had initial "group III" spinal fluids and most of whom had proved resistant to other forms of treatment. The incidence of clinical progression, even in this resistant group, was 9.5 per cent at five years with no further increase at ten years. Spinal fluid progression was not observed, and in 25 per cent of the cases the reaction of the spinal fluid became negative. Fever therapy with induced malaria thus was the most efficacious form of treatment in this type of asymptomatic neurosyphilis.

Anisocoria in Normal Persons.—Meyer [88] has studied 500 normal subjects with reference to the incidence of anisocoria and of differences of the width of the palpebral fissures. Nearly 17 per cent of the patients showed at least some degree of anisocoria, and in 4 per cent the difference in pupillary size was pronounced. Inequality of the palpebral fissures was even more frequent. Imbalance of sympathetic innervation and differences in refractive errors are considered to be possible explanations for at least some cases of anisocoria, but the author cautions that it should never be dismissed as an unimportant anomaly until a thorough search reveals no other etiologic basis for it.

Vertigo in Neurosyphilis.—Vertigo is rarely the presenting and only symptom of neurosyphilis. That occasionally it may be is evident from a recent report by Alpers.[89] In his 2 patients the vertigo was paroxysmal, severe and greatly influenced by changes in posture. In 1 patient temporary loss of hearing accompanied the attack of vertigo, but tinnitus was lacking in both cases. In the 2 cases there was a strongly positive reaction of the spinal fluid. It is considered that the vertigo resulted from an interstitial neuritis of the auditory nerve. One patient responded well to therapy with penicillin; the other failed to improve after administration of penicillin, but after therapeutic induc-

88. Meyer, B. C.: Incidence of Anisocoria and Difference in Size of Palpebral Fissures in Five Hundred Normal Subjects, Arch. Neurol. & Psychiat. **57**:464 (April) 1947.

89. Alpers, B. J.: Vertigo as the Presenting and Only Symptom of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:322 (May) 1947.

tion of malaria the vertigo disappeared and did not recur. The lack of audiometric and vestibular studies impairs the value of this report.

Primary Optic Atrophy.—McLean [90] has made follow-up observations on 30 patients treated for syphilitic primary optic atrophy. Neoarsphenamine and bismuth had been given to all the patients; in addition, tryparsamide had been administered to 27, and malaria had been induced in 21. The mean period of observation after treatment was seven and one-half years. On reexamination of the visual fields it was found that in 4 patients the atrophy had improved, in 23 it was unchanged and in 3 it was reduced. Ninety per cent of the patients had maintained their pretreatment visual acuity and visual fields.

Optochiasmatic Arachnoiditis.—Optochiasmatic arachnoiditis may produce a clinical syndrome not unlike that of tumor in the region of the optic chiasm or that of primary optic atrophy. This lesion has not been ascribed to any single cause. Trauma and localized leptomeningitis due to syphilis, mastoiditis, sinusitis, petrositis and chronic rhinopharyngitis have been described as etiologic factors. It has been described as a sequel of trauma, encephalitis and multiple sclerosis and tuberculosis, and it may coexist with Leber's disease and hydatid cyst. In many cases, however, the etiologic factor is not apparent.

Pendergrass and Perryman,[91] who present the case histories of 4 patients with chiasmatic arachnoiditis (1 of whom had syphilis), state the belief that the condition can be diagnosed by pneumoencephalography. They discuss the anatomy of the optic chiasm and certain of its contiguous structures from the standpoint of the roentgenologist. In the pneumoencephalogram it may be possible to demonstrate adhesions, cysts or obliteration of the cisternae in the region of the optic chiasm.

Tabes Dorsalis.—In tabes dorsalis, a study of the vibratory sensation as estimated with the tuning fork is a valuable diagnostic indication of damage to the posterior roots and posterior columns of the spinal cord. Borach [92] has studied the vibratory sensation quantitatively and has derived a normal curve based on the number of seconds' duration of the vibratory sense at each of eight bony prominences. In the normal person the sensitivity of the upper half of the body to vibration is greater than that of the lower half. Of the factors entering into the interpretation of the test, the author lists the following: 1. Vibratory sensation varies in different persons, some being more sensitive than others. 2. Vibratory sensation tends to diminish with advancing years. 3. For

90. McLean, J. A.: Visual Field Changes in Syphilis of the Central Nervous System, Canad. M. A. J. **55**:571 (Dec.) 1946.

91. Pendergrass, E. P., and Perryman, C. R.: Optochiasmatic Arachnoiditis, Am. J. Roentgenol. **56**:279 (Sept.) 1946.

92. Borach, J. H.: Test for Quantitative Vibratory Sensation in Diabetes, Pernicious Anemia and Tabes Dorsalis, Arch. Int. Med. **79**:602 (June) 1947.

some unexplained reason, the left side tends to be slightly more sensitive that the right side of the body. 4. Edema of the soft tissues interferes with the perception of vibration. 5. Paresthesias may confuse the results of the examination. In tabes dorsalis, the vibratory sensation was found to be strikingly lower than normal and to vary with the degree of damage at the time of examination. The level of the vibratory sensation was observed to rise as the patient's condition improved after successful treatment.

Charcot's Joints.—Historically, the etiology of that form of arthropathy known as Charcot's joint was the subject of a lively international controversy between the Frenchman, Charcot, and the German group of Volkmann and Virchow. Charcot believed that the changes in the joints were of a "trophic" nature whereas Volkmann took the position tha they resulted from a multiplicity of subclinical traumatic insults to the joint which went unperceived because of the insensitivity of the affected joints. Delano,[93] who recently reviewed the subject of the pathogenesis of Charcot's joint, found no definitive evidence for the existence of trophic nerves and concurs in the Volkmann-Virchow concept. Commonly associated with late neurosyphilis of tabetic type, Charcot's arthropathy may occur also in syringomyelia and, more rarely, in trauma of the spinal cord, trauma of the posterior roots or peripheral nerves, tumors of the cord, congenital malformations (such as spina bifida), tuberculosis or malignant spondylitis, acute myelitis, poliomyelitis and diabetic pseudotabes. Both atrophic and hypertrophic forms of neuropathic arthropathy occur. Delano states the belief that the most characteristic feature of neuropathic arthropathies is endochondral ossification. Concomitantly there is resorption and endochondral proliferation of the bone, with resultant incongruity of the surface of the joint brought about by repeated subclinical traumas occurring in an insensitive joint.

In severe, poorly regulated diabetes mellitus of long duration there may be neurologic changes that closely mimic those of tabes dorsalis (diabetic pseudotabes). Sensory disturbances, evidences of damage to the posterior column, areflexia and a predilection for the lower extremities are common to both conditions. In further illustration of how closely similar syphilitic and diabetic neuropathy may be, Foster and Bassett[94] report 2 cases of severe diabetes of long standing in which there developed cord bladders and neurogenic arthropathy of the Charcot type. These authors suggest that dysfunction of the

93. Delano, P. J.: The Pathogenesis of Charcot's Joint, Am. J. Roentgenol. **56**:189 (Aug.) 1946.

94. Foster, D. B., and Bassett, R. C.: Neurogenic Arthropathy (Charcot Joint) Associated with Diabetic Neuropathy, Arch. Neurol. & Psychiat. **57**:173 (Feb.) 1947.

autonomic nervous system is of significance in predisposing the skeletal system to an overreaction to trauma and the development of the Charcot joint.

Bailey and Root [95] report 17 cases of neuropathic arthropathy of the feet associated with diabetes mellitus. Each patient had destruction of the tarsal and metatarsal bones roentgenologically similar to that observed in Charcot joints. The most striking differences between the true Charcot joint and the diabetic neuropathic foot were the more acute onset of fluid in the joint and swelling of the extremity in the former, the presence of pain in the Charcot joint during the acute stage, the frequent occurrence of new bone formation in the Charcot joint and its rarity in the diabetic neuropathic foot, the occurrence of syphilitic osteosclerosis in areas near the involved joint, the physical evidences of tabes dorsalis in patients with Charcot joints and the relative infrequency of the true Charcot arthropathy in the feet.

Morris [96] also has observed neuropathic arthropathy of the foot in a patient with diabetes mellitus.

The Treatment of Lightning Pains in Tabes Dorsalis.—Costello [97] reports a favorable experience with the use of "protamide" [98] as treatment for tabetic lightning pains. This preparation, a colloidal suspension of processed and denatured proteolytic enzyme (pepsin), was found to be most satisfactorily administered intramuscularly without adjuvants. Injections were given once a week, and a course of twenty injections is recommended. The results of therapy in 89 patients are reported; 42 (47 per cent) are alleged to have obtained complete or almost complete relief of lancinating pains.

Pelner [99] reports relief of lightning pains and girdle sensations in 2 patients with tabes dorsalis following the intravenous injection of nicotinic acid.

Neurosyphilis in the Tropics.—It is a well known fact that neurosyphilis is rare in the tropics. Some have considered that this is so because of the common occurrence of malaria and other tropical fevers. McCartney,[100] however, notes that syphilis of the central nervous system is rare in the Marshall Islands, where there is no malaria. In this

95. Bailey, C. C., and Root, H. F.: Neuropathic Foot Lesions in Diabetes Mellitus, New England J. Med. **236**:397 (March 13) 1947.

96. Morris, M. H.: Charcot's Joint in Diabetes Mellitus, New York State J. Med. **47**:1395 (June 15) 1947.

97. Costello, R. T.: A New Treatment for the "Lightning Pains" of Tabes Dorsalis, Urol. & Cutan. Rev. **51**:260 (May) 1947.

98. Fuller Laboratories, Inc., 1275 Penobscot Bldg., Detroit.

99. Pelner, L.: The Treatment of Lightning and Girdle Pains in Tabes Dorsalis with Niacin, New York State J. Med. **47**:1496 (July 1) 1946.

100. McCartney, J. L.: Why Is Neurosyphilis Uncommon in the Tropics? Mil. Surgeon **99**:21 (July) 1946.

area, at least, it is considered that protection against neurosyphilis is afforded by coinfection with yaws, which is widely prevalent.

The relative significance of purely physiologic and emotional factors in the pathogenesis of the syndrome occurring after lumbar puncture has been studied by Redlich, Moore and Kimbell.[101] One hundred hospitalized psychotic patients were subjected to routine lumbar punctures. Alternate patients were punctured with number 16 and number 22 gage needles. These two groups were comparable with respect to diagnosis, age, sex and ratings as to intelligence, mood, emotional stability, chronic anxiety and hypochondriacal trends. Reactions in patients punctured by the larger needle were definitely more frequent, more severe and longer lasting than those among patients punctured with the 22 gage needle. This is interpreted as an indication that leakage of cerebrospinal fluid plays the major role in the production of headache after puncture.

The occurrence of symptoms had no significant relationship to the intelligence or emotional stability of the patients. Those with normal moods seemed to suffer severer headaches than those who were depressed or elated. The presence of chronic anxiety or hypochondriasis predisposed to a slight increase in incidence of complications, but there was no increase in the number of severe reactions. Unlike the intrinsic personality traits of the patients, which did not significantly affect reactions, a knowledge of ill effects in others and anxiety with regard to the procedure did increase postpuncture sequelae to a significant degree.

The authors conclude that drainage is the most significant factor in the production of symptoms after lumbar puncture, outweighing by far the small contribution of anxiety, hypochondriasis and other emotional elements.

The Outcome of Untreated Syphilis.—The end results of untreated syphilis are discussed by Rosahn[102] in the latest of his significant retrospective studies made at the Yale University School of Medicine. Among 380 syphilitic patients who were examined at autopsy at the New Haven Hospital in the period of 1917 to 1941 there were 198 (52.1 per cent) who had received no antisyphilitic therapy. Anatomic lesions of syphilis were found in 77 (38.9 per cent) of the untreated patients, but only 23.2 per cent of the entire group died primarily as a result of syphilis. Histopathologic evidences of syphilis were absent in 121 patients (61.1 per cent). Of these, 80 had serologic evidence

101. Redlich, F. C.; Moore, B. E., and Kimbell, I., Jr.: Lumbar Puncture Reactions: Relative Importance of Physiological and Psychological Factors, Psychosom. Med. **8**:386 (Nov.-Dec.) 1946.

102. Rosahn, P. D.: Studies in Syphilis: VII. The End Results of Untreated Syphilis, J. Ven. Dis. Inform. **27**:293 (Dec.) 1946.

of syphilis, and in 35 the reactions to serologic tests were negative during their last period of hospitalization.

A comparison of Rosahn's material with that of Bruusgaard [103] reveals a remarkable similarity. About 39 per cent of the former group of untreated syphilitic patients had postmortem evidences of syphilis, whereas in the latter group 35 per cent had clinical or postmortem lesions. In the Rosahn series 23 per cent died primarily as a result of syphilis, a figure identical with that found by Bruusgaard. Conversely, in the Rosahn series 61 per cent died with no anatomic evidence of syphilis, while Bruusgaard's group included 65 per cent who were without any evidence of organic syphilis. The ratio of positive and negative serologic results in the two groups is somewhat different, but this may be accounted for by (1) the large number of Bruusgaard's patients whose serologic status was not known and (2) probable differences in the sensitivity of the serologic tests employed in the two series.

This study affords further evidence that in a certain proportion of infected persons (17.7 per cent in Rosahn's material) defense mechanisms of the host suffice to effect spontaneous cure of the disease in the absence of treatment of any kind.

The data of Deibert and Bruyere [104] suggest that in the absence of specific treatment patients with syphilis, even though they may escape the crippling late manifestations which eventuate in death, still run a not inconsiderable risk of having their life span shortened. It is further suggested that infected persons will experience more manifestations of general ill health than will those who have never had syphilis.

Immunity and Allergy in Syphilis.—Taking the point of view that penicillin may afford a new avenue to the understanding of the nature of immunity in syphilis, Urbach and Beerman [105] have reviewed the present status of immunity and allergy in syphilis. Their review does not readily lend itself to condensation. Exception might readily be taken to its primary premise. In summary it is concluded that:

1. Since penicillin has an apparent capacity to cure experimental and human syphilis quickly and completely, new fields for the experimental study of immunity in this disease are opened. This fact warrants critical reevaluation of the present status of immunity and allergy in syphilis.

2. According to the viewpoint adopted in this review, allergy is a comprehensive term which may be expressed as hyper- or hyposensitiveness, while immunity is a special form of allergic hypersensitiveness.

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103. Bruusgaard, E.: Ueber das Schicksal der nicht spezifisch behandelten Luetiker, Arch. f. Dermat. u. Syph. **157**:309, 1929.

104. Deibert, A. V., and Bruyere, M. C.: Untreated Syphilis in the Male Negro: III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J. Ven. Dis. Inform. **27**:301 (Dec.) 1946.

105. Urbach, E., and Beerman, H.: The Present Status of Immunity and Allergy in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:192 (March) 1947.

3. In syphilis there are two types of immunity; (*a*) natural resistance and (*b*) acquired immunity. Human beings are naturally susceptible to syphilis, while many species of animals previously thought to enjoy natural resistance are really susceptible but acquire only an asymptomatic infection.

4. All authorities agree that variable grades of immunity develop in syphilitic animals and man; but opinion is divided as to whether this immune state depends on persistence of infection (Neisser, Kolle) or whether it is independent of it (Chesney).

5. Under certain experimental conditions and taking account of the various modifying factors, the untreated animal, as determined by the results of reinoculation, acquires resistance to a second infection slowly. During the early phases of the disease untreated animals are wholly receptive to a new infection, later they are not. In animals treated early, prior to the development of immunity, second infection is manifested by chancre formation. Energetic treatment in late syphilis will protect the animals against reinfection. It is suggested that a controlled repetition of these experiments, using penicillin as the means of cure of syphilis because of its rapid excretion, would throw light on the nature of syphilis immunity.

6. Attempts to superinfect untreated syphilitic individuals with massive inoculums are often successful. This indicates that their immunity is at best only relative in all phases of the disease. This fact brands efforts to immunize syphilitics with virulent treponemes as potentially dangerous.

7. Intensive treatment of early syphilis will probably cure the disease. Though such treatment abolishes developing immunity, it does not subject the patient to danger if the treatment completely eradicates the disease. If therapy is inadequate, it leaves the patient in a vulnerable position since the developing defenses are disturbed and the patient is not cured. This state often results in various forms of therapy-resistance or seroresistance.

8. The mere fact that a patient may be reinoculated successfully with syphilis does not indicate that he has been cured. On the other hand, completely cured individuals may remain refractory to reinfection.

9. In patients treated early in the course of syphilis, reinfection does not indicate cure since it may be possible that the new infection could be superinfection. We have no adequate means of differentiation between reinfection and superinfection.

10. Allergy and immunity are not mutually exclusive, but immunity is a special aspect of allergy. This viewpoint is upheld by various experimental studies. The entire course of syphilis may be explained on the basis of allergy. The reaction of the organism to reinfection also suggests an allergic mechanism. Attempts to develop a method to determine the allergic state of a syphilitic individual have led to little of a definite nature. While culture luetin is diagnostically worthless, reevaluation of organic luetin is suggested.

11. The question of the existence of antibodies against syphilis is still unanswered, but recent work suggests a cellular defense. The relationship of the positive serologic reaction to the organism's capacity to produce antibodies against spirochetes is not clear.

12. Numerous attempts to induce active or passive immunization against syphilis in man and animals have to date failed to produce any significant results. This applies both to prevention of the infection as well as to the treatment of an established syphilitic infection."

(*To Be Continued*)

Book Reviews

A Textbook of Clinical Neurology. By J. M. Nielsen, M.D. Second edition. Price, $7.50. Pp. 699. New York: Paul B. Hoeber, Inc., 1946.

Dr. Nielsen's "Textbook of Clinical Neurology" was published first in 1941; the revised second edition appeared in 1946. The author aimed to present the subject of clinical neurology in a volume sufficiently small that it could be used as a text of the subject during the time allotted to neurology in a general medical course. His goal has been accomplished and surpassed.

The routine material to be found in any good textbook of neurology is presented in most instances with acceptable detail. Comprehension of each subject is enhanced by discussions of the pertinent basic material in anatomy, physiology, pathology and pharmacology. Clinical appreciation of the subjects is increased by the author's creditable selection of brief case reports interspersed throughout the book. The book is well illustrated, well indexed and pleasingly made up. Furthermore, it is remarkably up-to-date. There is full discussion of the use of penicillin and sulfonamide compounds in the treatment of neurologic disorders.

The book is of particular importance because of the excellence of the material regarding cerebral localization and syndromes of the brain stem. Dr. Nielsen is an outstanding authority on aphasia, agnosia and apraxia. Only a thorough scholar could present these difficult subjects with the clarity and conciseness with which they are discussed in this book. Because of this fact, the textbook has surpassed the author's aim and will find its place in the reference library of actively practicing neurologists.

This book can be recommended without hesitation for medical students and for practitioners of medicine and surgery. Because it contains an excellent digest of the total information available on the subjects of agnosia, apraxia and aphasia, the specialists in neurology, neurosurgery and psychiatry will find it invaluable as a reference work.

Medicine in the Changing Order. Report of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, $2. Pp. 258. New York: Commonwealth Fund, 1947.

The committee of thirty-three physicians and seventeen representatives of allied professions and lay persons first convened on Feb. 25, 1943, and in a period of a little over three years has held one hundred and twenty-three meetings and has obtained information and opinion from a wide variety of authorities who "represented every shade of economic, social and political conviction that might have a bearing on medical care."

At the outset, the objectives were defined: "To be informed of the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and in the services to the public may be preserved and embodied in whatever new social order may ultimately develop."

The report is condensed into twelve chapters, which begin with a historical discussion of the origins of the present problems in American medicine, particularly in recent decades, and go on to a discussion of the health of the nation, medical care in urban and in rural areas, extension in public health services, quality of medical care, preventive medicine, the hospital, nursing, medical insurance—voluntary and compulsory—and a final statement of the methods and the goal.

The committee is to be commended for its broad-gaged study of this most complex and vital problem and also for its soundness in the formulation of recommendations which deserve the full support and careful consideration of all the members of the medical profession.

Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment. Edited by Garfield G. Duncan, M.D. Second edition. Price, $12. Pp. 1045, with 167 illustrations. Philadelphia and London: W. B. Saunders Company, 1947.

It is difficult to circumscribe that part of medicine which deals with metabolism. Metabolism includes all those processes by which matter, be it organic or inorganic, is utilized for the growth, repair and maintenance of the organism. The processes comprehend intake of food, including minerals, water and other factors, such as vitamins; transportation of oxygen, and the manifold chemical transformations of organic materials whereby energy is released as heat and the activities of muscles, nerves and glandular organs are maintained and waste products are disposed of by excretion through lungs, kidneys, skin and bowel. Therefore every field of medicine is invaded, and, in truth, as the search for understanding of the metabolic abnormalities in disease and injury has extended, light has been brought to bear on obscure problems of each of the several specialties of medicine and surgery.

Duncan and the outstanding collaborating authors have provided in this volume a satisfactory appraisal of the present state of knowledge of the metabolic aspects of disease. The scientific background is adequately reviewed, but such material as has little practical application at the present was omitted in this second edition. Emphasis is placed on the significance of metabolism in diagnosis and treatment, and yet the bridging of the gap between the scientist and the physician is adequately effected.

Duncan is himself responsible for the chapters on exchange of energy (general and basal metabolism), diabetes mellitus, hyperinsulinism and diabetes insipidus. The metabolism of sugar and other carbohydrates is reviewed by C. N. H. Long and that of protein and the lipids by Abraham White. Mineral metabolism is discussed by Abraham Cantarow. His chapter also covers hyperparathyroidism and hypoparathyroidism, adrenocortical insufficiency (Addison's disease) and adrenocortical hyperfunction. Water and acid-base equilibrium are reviewed by John P. Peters, with special attention given to edema, the salt depletion of pneumonia, the nature of "shock" and the effects on salt and water metabolism of heart failure, disease of the kidneys and disease and disorder of the gastrointestinal tract.

The diagnostic problems presented by diseases of the blood are largely morphologic, but the etiology and treatment of many of these diseases present problems of nutrition and metabolism. The diseases of the blood receive consideration from this aspect by L. M. Tocantins. Vitamins and vitamin deficiencies are reviewed by T. D. Spies and H. R. Butt; undernutrition is discussed by L. H. Newburgh, and obesity, by Frank Evans. The chapter on gout is by Walter Bauer and Frederick Klemperer, and the one on xanthomatosis, glycogen disease and other disturbances of intermediary metabolism, alkaptonuria, porphyria and the like is by E. U. Mason.

The inclusion of two new chapters in the second edition of this volume, one dealing with the thyroid by Alexander Winkler and the other with the diseases of the kidneys by Max Miller and Joseph Hayman, may be of doubtful wisdom. The chapters are well written, but to the extent that the material involves metabolic abnormality it represents some repetition of what appears in other chapters and to the extent that it involves morphology it may be out of place in such a book as this. At least as good a case might be made for adding chapters on diseases of the liver, on pregnancy, on growth and development in childhood and on diseases of the nervous system with components which are metabolic.

The first edition of this book was well received. The second edition brings the subjects up to date and can be highly recommended. Charles Best has stated in its foreword that "we are at the threshold of what may prove to be a great new era in metabolic and other aspects of medical research. It is essential, therefore, for us to make critical appraisal of our present knowledge of metabolic processes. There is no doubt that we have a firm foundation on which to build, and many lofty structures have already been erected. A few, however, may be picturesque but unsound, and a review of the situation such as that provided in this new edition of 'Diseases of Metabolism' comes at an opportune time."

Medical Aspects of Growing Old. By A. T. Todd, M.B. Price, 15s. Pp. 172. Baltimore and Bristol, England: John Wright & Sons, 1946.

It seems recently to have become the fashion for medical men of a certain age to emulate Cicero and write about old age. Considerable geriatric literature has accumulated on this side of the Atlantic; here is a British sample.

The author writes pleasantly on the medical aspects of growing old and, on the whole, tends to show that the experience of adding years to one's life may be made into an amiable adventure if it is handled properly. He gives sensible advice in regard to the care of ancient hearts, blood vessels and digestive tracts and even of well worn hands, feet and skin. He has a nice philosophy, well expressed. He has prepared an attractive monograph which both patients and their physicians can study with profit.

Précis de virologie médicale: Vaccine-variole, herpès, encéphalites, rage, poliomyélite, chorio-méningite, fièvre jaune, psittacose, influenza, maladie de Nicolas et Favre, nature et genèse des ultravirus, techniques. By C. Levaditi. Paper. Price, 235 francs. Pp. 250, with 142 illustrations. Paris: Masson & Cie, 1945.

This book has as its main purpose the condensed presentation of the knowledge on the most important virus infections of man, followed by a discussion of the nature of viruses. A chapter of thirty-six pages on the technics employed in the study of virus infection is too concise and incomplete to be useful. Although it goes into detail about stains and staining solutions, the use of filters and method of infection, it completely ignores the serologic diagnostic procedures. There is no bibliography except an occasional footnote referring the reader to the handbook "Les ultravirus des maladies humaines," published in 1938 by the same author in collaboration with P. Lépine.

In accordance with the well known views of the author, the infections are grouped under the following headings; pure ectodermoses (vaccinia), neurotropic ectodermoses (herpes, encephalitides), neuroses (rabies, poliomyelitis), neuro-organotropic virus diseases (yellow fever), viscerotropic virus diseases (psittacosis, influenza) and mesodermotropic virus diseases (lymphogranuloma).

The author's theories are given prominence. For example, he concludes that postvaccinal encephalitis is a complication brought about in predisposed persons by the localization of an unknown virus in the central nervous system. The allergic phase present in vaccination is considered to be particularly favorable to the encephalic genesis of the process. The discussion of herpes simplex overlooks the present day knowledge of the ecology of this virus. On page 136 Levaditi dogmatically says: "It is certain that the virus of poliomyelitis invades the body through the upper respiratory tract and, in particular, the nasopharyngeal mucosa, and it is likewise eliminated through this mucosa."

More than twenty-one pages are devoted to a presentation of the subject of *ultravirus lymphogranulomateux (maladie de Nicolas et Favre)*, while the discussion on influenza covers but eight pages. Equally brief is the chapter on yellow fever, which incompletely reports the fascinating epidemiologic studies on jungle yellow fever. In fact, the whole treatise is singularly deficient in epidemiologic thinking. But such criticism is really immaterial, because the merit of the compendium lies in the summary presentation which acquaints the reader with the rapidly growing field of virus agents that are believed to cause infections or infectious diseases.

Until a similar up-to-date book in the English language is available, students and physicians may enjoy this presentation of the subject.

On the Morphology of Blood and Bone-Marrow in Thyrotoxicosis. Inaugural Dissertation. By O. Biström. Pp. 188. Acta chirurgica Scandinavica, volume LXCIV, supplementum 114. Stockholm: Norstedt & Söner, 1946.

This monograph is a report of the condition of the blood and of the bone marrow obtained by aspiration in 24 control subjects, 26 patients with nontoxic goiter and 33 patients with thyrotoxicosis. The older literature is completely reviewed; practically no investigations have been reported on the bone marrow in thyrotoxicosis.

The patients with nontoxic goiter showed no important abnormalities. The more important deviations in the patients with thyrotoxicosis consisted of a lymphocytosis of the peripheral blood and a shift toward immaturity of the neutrophilic granulocytes and, to a lesser extent, of the normoblasts in the bone marrow. This shift was more distinct in the severely toxic forms of the disease. The described changes reverted toward normal after therapy with iodine or methylthiouracil and after thyroidectomy. The author does not feel that the inconstant and slight changes in the blood and bone marrow are of great importance in the prognosis and diagnosis of thyrotoxicosis. The monograph should be a useful reference for workers in this field.

La cultura in vitro del midollo osseo. By Aminta Fieschi and Giovanni Astaldi. Pp. 309, with 122 illustrations, 10 in color. Pavia, Italy; Tipografia del Libro di S. Bianchi, 1946.

A new technic of culture suspension of heparinized bone marrow is suggested. It consists in the use of a simple apparatus that permits a regular supply of oxygen and nutritive material to the cultured marrow. Tyrode's solution is homologous fresh plasma and extraction of chicken embryo circulated through a system in which waste products are removed. Cultures of normal and abnormal human bone marrow have been carried out with this technic.

When normal bone marrow is so cultured, it may be observed that in the first eight to fifteen days both specific marrow cells and fibroblasts are present in the tissue and will survive and show signs of moderate proliferation. In the second

period, indefinite in time, only the fibroblastic elements survive and start a copious proliferation, as they are by then completely adjusted to the new medium. The proliferative and maturative changes of the specific elements are particularly evident in the surviving cells of the erythroblastic and granuloblastic series. Parent cells of the monocytic and lymphocytic series and megakaryocytes, however, do not show any tendency to proliferation.

The main feature of this work is represented by the developed technic, which is particularly promising of results in the study of several known and unknown factors in the evolution and proliferation of living marrow elements.

Le malatte del sangue (Pathology of the Blood). By A. Ferratta, M.D., and E. Storti, M.D. Price not stated. Pp. 751, with 295 illustrations. Milan, Italy: Societa Editrice Libraria, 1947.

This manual, while written by two Italian physicians, might well have been prepared for American readers. Perhaps it merely reveals the international uniformity of medical opinion now existing in regard to the diagnosis and treatment of the various disorders of the blood. In either event, the result is satisfactory.

The book begins with an account of how blood is formed and how it functions. It next discusses finer points regarding blood counting. This is followed by excellent descriptions of bone marrow histology, blood transfusion, blood typing and methods of estimating the sedimentation rate. Most of the volume, however, deals with matters that are more strictly clinical in nature. The anemias, the leukemias and the reaction of the blood-forming organs to onsets of varying kinds are discussed in detail, both diagnosis and treatment receiving ample consideration. Many exceptionally good illustrations and colored plates embellish the text and make it all the easier to understand.

The end result is an attractive textbook. It is certain to be appreciated by the physicians and medical students for whose benefit it was composed.

A Color Atlas of Hematology. By Roy R. Kracke, M.D. Price, $5. Philadelphia: J. B. Lippincott Company, 1947.

As stated in the preface, this book was prepared especially for the use of medical students, laboratory technicians and general practitioners. The author has achieved his purpose in an eminently satisfactory manner. Although the volume has been kept to a small, convenient size, all the important variations in both normal and abnormal blood pictures are shown in the 32 color plates. Adding greatly to the usefulness of this type of atlas is a concise, systematic clinical discussion of the various blood diseases. Valuable chapters have been included on hematologic technics, the bone marrow, blood parasites, splenomegaly and splenectomy, the blood picture in various laboratory animals, hematologic definitions and, finally, a "summary of hematologic findings in various diseases and conditions."

This is an excellent practical atlas and concise summary of present day hematology by a recognized authority. It should prove of value to all those concerned with this subject.

Biological Symposia: A Series of Volumes Devoted to Current Symposia in the Field of Biology. Volume 12: Estimation of the Vitamins, edited by J. D. Dann and G. Howard Satterfield. Price, $6.50. New York: The Ronald Press Co., 1947.

This is an advanced book for the specialist. It consists of a series of articles by experts describing in technical terms the various methods of vitamin assay—

chemical, biologic and microbiologic. There are comprehensive bibliographies. This treatise should be invaluable to those working in the special field of vitamin measurements, since not only is theory discussed but minute directions for the practical procedures are given.

Urology in General Practice. By N. F. Ockerblad, M.D. Second edition. Price, $5.75. Pp. 392, with illustrations. Chicago: Year Book Publishers, Inc., 1947.

This little treatise attempts to present in simple terms the problems of urology which confront the general physician. Special problems of surgical technic and the like are not gone into. The discussions are brief and simple and to the reviewer seem useful. For example, a chapter on "catheters and sounds—their uses and dangers" can surely be read with profit. Some of the material on medical problems, such as nephritis, is sketchy and perhaps less useful. The book is well illustrated and has an index.

Diseases of the Chest with Emphasis on X-Ray Diagnosis. By Eli H. Rubin, M.D. Price, $12. Pp. 685, with 355 illustrations. Philadelphia: W. B. Saunders Company, 1947.

This treatise discusses comprehensively the various diseases which affect the structures within the chest. Thus there are included not only such processes as tumors, abscess and bronchiectasis but also conditions like acute pneumonia and bronchial asthma. Pulmonary tuberculosis is thoroughly gone into, although only a small paragraph is devoted to streptomycin, which is so much to the fore today. The anatomy and physiology of the lungs are adequately discussed, and the sections on surgical procedures are useful. As Dr. Rubin points out, roentgen diagnosis is emphasized, and there are over three hundred admirable reproductions of roentgenograms dealing with every sort of pulmonary disease. This is an unusual and certainly invaluable feature of the book.

Asma alergia. By Guido Ruiz Moreno, M.D. Pp. 186. Buenos Aires, Argentina: Lopez & Etchegoyen, S. R. L., 1947.

This book has been written for students as an introduction to the more extensive textbooks on the subject and for general practitioners as a contemporaneous orientation.

The work is divided into two parts. The first section is devoted to a discussion of asthma. The definition, classification, physiopathology, symptomatology and etiology of the asthmatic states are discussed. There are also in this section discussions on the diagnosis, prognosis, treatment, complications and sequelae of asthma. The author included in this section a discussion of asthma as a problem in social medicine. In the second part the definition, concept and classification of allergies are discussed. There are brief general discussions on the clinical aspects of allergic diseases.

Each chapter is followed by a brief outline in which the essentials of the particular subjects are summarized. Dr. Moreno's observations on asthma and the clinical allergies have been made in Argentina and should prove of definite value to the physicians of that country.

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